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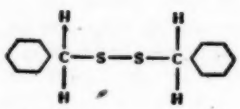

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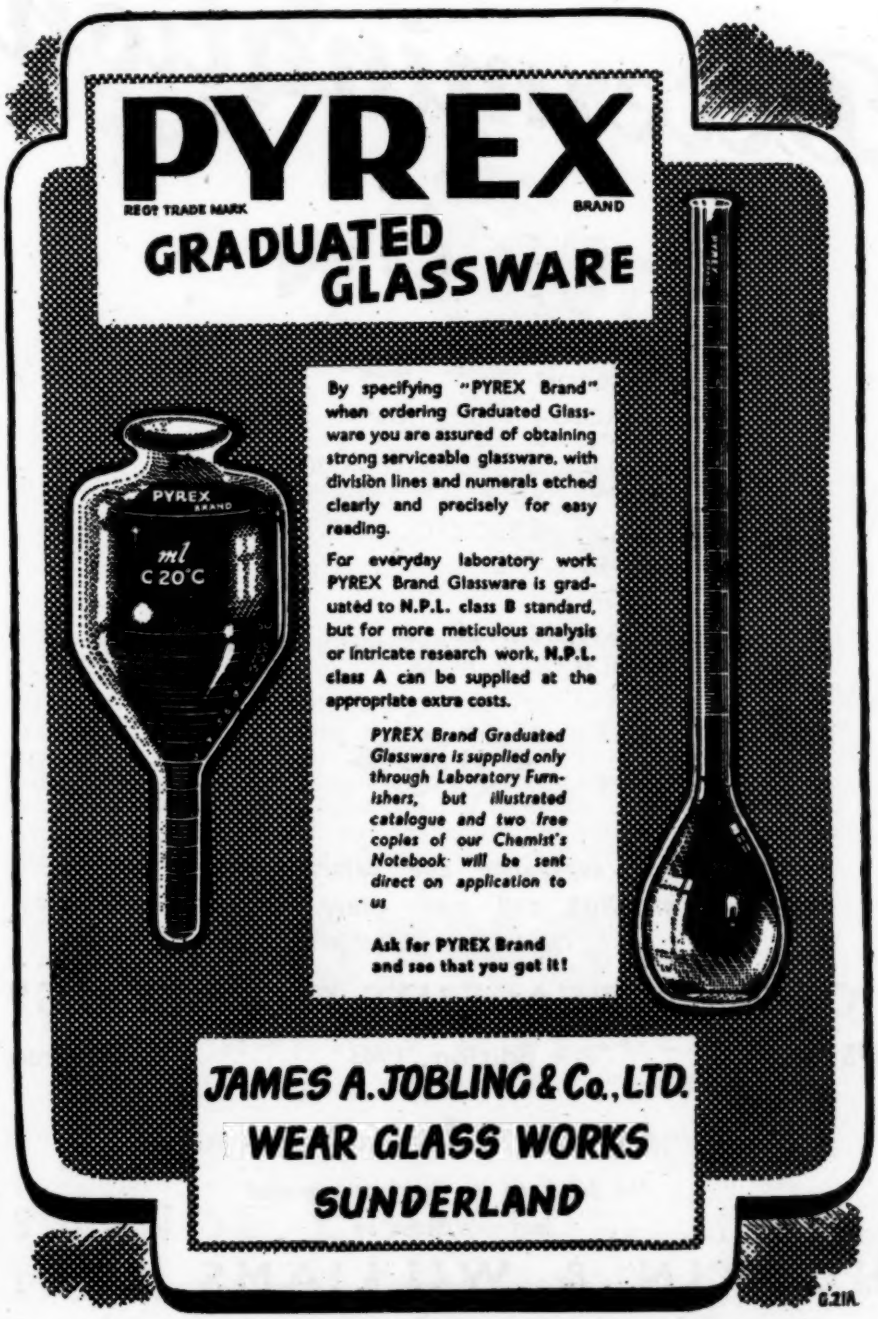
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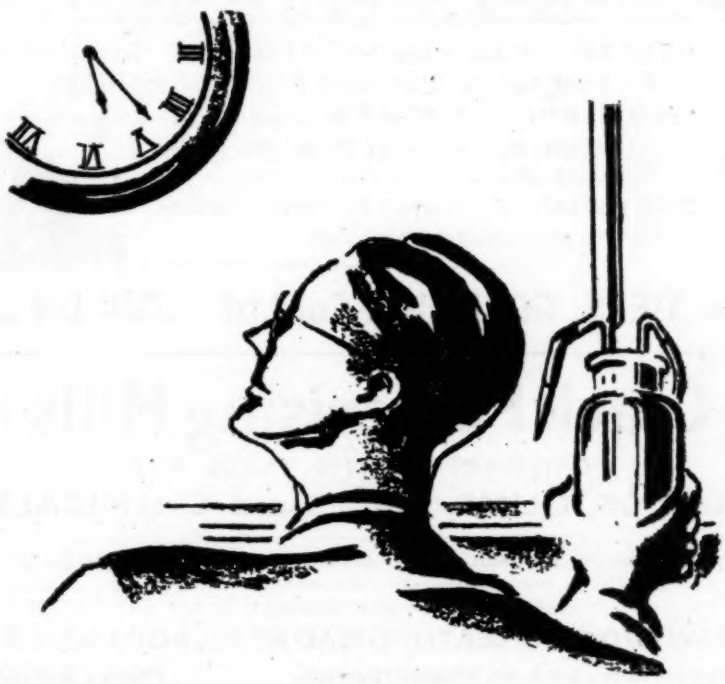

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and palladium-black (0·1 g.) until absorption ceased. The saturated ester was not obtained crystalline and was hydrolysed by boiling alcoholic potash to *cis*-indane-1 : 2-dicarboxylic acid, m. p. 228° (1·4 g.). In all, 20·5 g. of this acid were obtained from 30 g. of the unsaturated ester. A suspension of the saturated acid (6·7 g.) in acetyl chloride (30 c.c.) was boiled for 6 hours. The solvents were removed, and the residue distilled from an air-bath at 145°/0·2 mm. The distillate (3·5 g.) crystallised on standing, and recrystallised from benzene–*cyclo*hexane in colourless plates of cis-*indane*-1 : 2-*dicarboxylic anhydride*, m. p. 97—98° (Found : C, 70·4; H, 4·1. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3%). This anhydride, which must be derived from the *cis*-acid, is hydrolysed to the acid, m. p. 228°, from which it was prepared. The latter therefore has the *cis*-configuration. The anhydride reacts with alcohol to give the *monoethyl* ester, m. p. 123—124° (Found : C, 67·1; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

We are much indebted to Imperial Chemical Industries Ltd. (Dyestuffs Division) for financial provision which has enabled one of us (R. W. G. P.) to carry out the experiments here recorded, and also for gifts of chemicals. All analyses were micro-analyses carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, June 26th*, 1944.]

NOTE.

The Preparation of 1 : 2 : 3-*Trinitronaphthalene.* By HERBERT H. HODGSON and DAVID E. HATHWAY.

THE ease with which toluene-*p*-sulphon-1-naphthalide is dinitrated in the 2- and the 4-position (Hodgson and Walker J., 1934, 180) has been utilised for the preparation of 2 : 3 : 4-*trinitrotoluene*-p-*sulphon*-1-*naphthalide* from 3-nitrotoluene-*p*-sulphon-1-naphthalide (Hodgson and Hathway, this vol., p. 21). Homonuclear dinitration was established by oxidation of the above compound to phthalic acid with neutral aqueous potassium permanganate. Subsequent hydrolysis by concentrated sulphuric acid to 2 : 3 : 4-*trinitro*-1-*naphthylamine* (cf. Hodgson and Birtwell, J., 1943, 433), diazotisation by Hodgson and Walker's procedure (J., 1933, 1620), and decomposition by cuprous oxide in ethyl alcohol (Hodgson and Turner, J., 1942, 748) afforded 1 : 2 : 3-*trinitronaphthalene*.

Dinitration of 3-*Nitrotoluene*-p-*sulphon*-1-*naphthalide*.—Nitric acid (3 c.c., *d* 1·42) in which a crystal of sodium nitrite had been dissolved, was added with vigorous stirring at 50° to a finely divided suspension of 3-nitrotoluene-*p*-sulphon-1-naphthalide (6 g.) in glacial acetic acid (12 c.c.), and the mixture heated to 75°; dinitration then occurred, the temperature rising to 100°. On cooling, 2 : 3 : 4-*trinitrotoluene*-p-*sulphon*-1-*naphthalide* (4 g.) slowly crystallised in fine, cream, felted needles, which were filtered off, washed successively with glacial acetic acid, methyl alcohol, and ligroin, and finally dissolved in hot glacial acetic acid, from which it crystallised on cooling in buff-coloured rods, m. p. 190° (Found : N, 12·95. $C_{17}H_{12}O_8N_4S$ requires N, 12·96%).

Orientation of the Nitro-groups. The trinitro-compound (1·2 g.) was boiled for 5 hours with a solution of potassium permanganate (3·5 g.) in water (50 c.c.). Sulphur dioxide was then passed through the chilled acidified solution to dissolve the manganese oxides, and the mixture was heated, filtered from insoluble organic material, and the filtrate evaporated to dryness; the residue of crude phthalic acid was purified by dissolution in ether, removal of the ether from the extract, and crystallisation of the residual phthalic acid from hot water; m. p. and mixed m. p. 195°.

2 : 3 : 4-*Trinitro*-1-*naphthylamine* was formed when a cold solution of the naphthalide (1 g.) in sulphuric acid (5 c.c., *d* 1·84) was heated at 30° for 15 minutes, the mixture poured on ice, triturated with aqueous ammonia, and the free amine (0·7 g.) removed; it crystallised from ethyl alcohol–acetone (1 : 2) in orange-yellow, micro-crystals, m. p. 220° (Found : N, 20·3. $C_{10}H_5O_6N_4$ requires N, 20·2%).

1 : 2 : 3-*Trinitronaphthalene*.—The trinitro-naphthalide (1·3 g.) was stirred into sulphuric acid (7 c.c., *d* 1·84) below 10°, a solution of sodium nitrite (0·3 g.) in sulphuric acid (2 c.c., *d* 1·84) added, and the mixture stirred into glacial acetic acid (25 c.c.) below 20°. Stirring was continued for 30 minutes, after which the diazotised solution was stirred into a suspension of red cuprous oxide (0·8 g.) in ethyl alcohol (50 c.c.). After the reaction had subsided, the mixture was poured on ice (300 g.), filtered, the filtrate steam-distilled to remove volatile compounds, and the flask liquor extracted with ethylene dichloride (100 c.c.) to remove the 1 : 2 : 3-trinitronaphthalene, the extract being washed with aqueous sodium carbonate followed by water. On partial removal of the ethylene dichloride from the dried extract, the 1 : 2 : 3-*trinitronaphthalene* (0·3 g.) was deposited; it recrystallised from chloroform in pale orange parallelepipeds, m. p. 190° (Found : N, 16·0. $C_{10}H_5O_6N_3$ requires N, 16·0%). This compound can be sublimed, and also gives a blood-red colour with aqueous acetone containing sodium hydroxide, but no pronounced coloration with alcoholic potassium hydroxide.

The authors thank Imperial Chemical Industries Limited, Dyestuffs Division, for gifts of chemicals.—TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, August 24th*, 1944.]

OBITUARY NOTICES.

HORACE EDWARD BROTHERS.

1863—1944.

HORACE EDWARD BROTHERS died at his home at Old Colwyn on July 3rd, 1944, in his 81st year.

He was a son of the late Alfred Brothers of Manchester, a pioneer of astronomical photography, whose photographs of the solar eclipse at Syracuse in 1870 showed that the corona is an appendage of the sun.

Brothers received his early education at Alderley Edge, and at Chorlton High School, Manchester. From 1881 to 1885, he attended Owens College, studying chemistry under Roscoe and Schorlemmer, and physics under Balfour Stewart. He took a new course of studies specially designed to qualify for a technical position in industry at a time when the employment of scientifically trained men by manufacturers was rare. From 1885 to 1899 he was analyst and technical manager of a chemical works in the Potteries, engaged in the extraction of cobalt and nickel and their compounds, and in the manufacture of borax and boric acid.

In 1899 he became one of H.M. Inspectors of Factories, and in 1903 was deputed to investigate chemically the means of ventilation, and effects of artificial illumination in workrooms in the flax and jute works in Scotland. He also took part in a special enquiry into the dangers peculiar to chemical industry, and the most effective means for prevention of accidents to workers in these factories. The enquiry led to the drawing up of a code of " Regulations for Chemical Works " issued by the Home Office Factory Department in 1922. These Regulations still prove effective, and many of their requirements have been embodied in the new Factory Act of 1938.

Brothers retired from the Civil Service in 1925. He was a Fellow of the Royal Institute of Chemistry, a Fellow of the Chemical Society for nearly 60 years, and a life Member of the Society of Chemical Industry. He was a joint author of a paper on phenolic constituents of blast furnace tars published in the *Journal* in 1886.

(MISS) D. M. BROTHERS.

DAVID GWYNNE DAVIES.

1907—1944.

DAVID GWYNNE DAVIES died in tragic circumstances at Malvern on April 16th, 1944. He was the only son of Mr. J. R. Davies, sometime Headmaster of Dowlais Boys' School, Merthyr Tydvil, and was educated at his father's school and at Merthyr Tydvil Intermediate School. In 1925 he entered the University College of Wales, Aberystwyth, as a student in the Teacher's Training Department and graduated B.Sc. in 1928 with Second Class Honours in Chemistry. After completing the Diploma in Education, he pursued a course of research under the direction of Mr. C. R. Bury and was awarded the Ph.D. degree in 1931. Their work is published as a series of papers in the *Journal*.

Subsequently Davies was appointed Assistant-Lecturer in the Department of Chemistry at his College, where he proved to be a very capable teacher and research worker. Becoming interested in the study and teaching of micro-analytical methods, he assisted in the foundation of the Microchemical Club. In 1934 he became an officer in the College contingent of the Officers' Training Corps and in 1936 succeeded to the command. At the outbreak of war he organised and commanded the University of Wales (No. 2) Reception Unit at Cardiff and subsequently served with a training unit of the South Wales Borderers. He returned to Aberystwyth in 1940 to command the Senior Training Corps, in which he attained the rank of Major, and to resume his teaching work in the department of Chemistry. In carrying out these duties in the service of the associated University Colleges of London and Wales with efficiency and tact, he earned the commendation and gratitude of both institutions

T. CAMPBELL JAMES.

JOHN SIMPSON FORD.

1866—1944.

JOHN SIMPSON FORD was born in Edinburgh in 1866 and died there on March 27th, 1944. He was educated at the Royal High School and University of Edinburgh. Before entering the latter, however, he had spent three years as an articled pupil of Falconer King, Public Analyst, during which time an inclination to take up medicine appears to have developed, for he went up to the University for that purpose. His success at Chemistry, however, led to his studying the subject under Professor Crum Brown, winning the Hope Prize in Chemistry.

In 1889 he was appointed chemist to Messrs. William Younger and Co., Ltd., and there he remained as chief chemist and afterwards as technical director until his death. A little time spent in Copenhagen under Jörgensen in 1893 led to an attempt by him to apply Hansen's single cell yeast technique to Scottish top fermentation brewing. The use of yeast grown from a single cell led to complications, as more than one

race or strain was needed to fulfil all the requirements of the Scottish brewing process. The fundamental problem arose as to whether greater importance should be attached to the selection of a race of top yeast or to the influence of environment on the selected race. In this case the chief factor in the environment was the chemical composition of wort. Ford's predilections were those of the chemist and he rightly considered on the evidence of his work that the environmental factors predominated.

In the early years of the century Ford was responsible for a number of papers on analytical methods, malt, Lintner soluble starch, etc., which appeared in the *Journals* of the Society of Chemical Industry, the Chemical Society, and the Institute of Brewing. But his best work was on malt diastase, and was mainly concerned with the influence of hydrogen and hydroxyl ions on the rate of action of the enzyme, and the stabilising effects on asparagin and phosphates—now recognised as pH buffers. It is clear that Ford was thinking in terms of hydrogen-ion concentration and buffer substances, although the convenient formulation of the pH scale by Sörensen and the widespread adoption of these ideas was not to take place for some years. Probably his best paper was the one with J. M. Guthrie read to the Institute of Brewing under the title " Contributions to the Biochemistry of Barley " (1908). In it evidence was furnished that the amylase of resting barley is largely inactive, probably bound to protein. This notion of a stock of enzyme formed during ripening and " fixed " in a stable inactive form in the resting corn, from which it could be liberated or activated when required, contributed usefully to the concept of a zymogen which was at that time being developed by Bayliss and others in respect of enzymes of the digestive tract. Even within recent years experimental work leading to mutually antagonistic hypotheses has been performed on the amylases of grain by Chrzaszcz and Myrbäck. From it one can conclude that the accuracy of Ford and Guthrie's experimental work and the soundness of their deductions remain fully established in the light of modern work.

During the first world war Ford served as a Lieutenant in the R.A.S.C., and in 1921 became a technical director to his firm. With the exception of papers (with Tait) on the determination of antiseptic value of hops and (with Fletcher) on brewing trials with new hybrid varieties of hops, Ford's later contributions to science and technology appear in the form of very many papers inspired by him but contributed by members of his staff, particularly Tait and Fletcher, to the *Journal* of the Institute of Brewing. However, a final paper from Ford appeared in 1941 on the occasion of the presentation to him of the " Horace Brown Medal " by the Institute of Brewing. Of necessity much of his work was not published.

Ford was possessed of the spirit of the investigator. He relied only on experimental evidence and sought it whenever possible. In drawing conclusions to his observations he always remained fully alive to alternative hypotheses.

He was a Fellow of the Chemical Society, the Institute of Chemistry, Royal Society of Edinburgh, original member of the Biochemical Society, for three years Chairman and honorary director of the Institute of Brewing's research.

His chief hobbies and recreations were motoring, photography, gardening, and, in early life, cycle racing, at which he won many medals. He was an indefatigable worker and a great source of inspiration and encouragement to his staff.

R. H. Hopkins.

FRANK LEE PYMAN.

1882—1944.

Frank Lee Pyman died on January 1st, 1944, in his sixty-second year. The traits of character that made his contributions to organic chemistry and to chemotherapy important were his persistence in the experimental attack of a problem from varied avenues of approach and his insistence that all observed facts must be accounted for by reasoning. Moreover, he always seemed to carry with him a great store of energy ready to be disseminated in endeavouring to reach the truth relating to any problem that interested him and he was able to think with lightning speed.

As a teacher and in the directing of research, the successes he achieved are to be attributed largely to these qualities combined with insistence on a high standard and businesslike ways and habits. His influence was augmented by the purposeful ends to which his researches were directed, for whether in the unravelling of chemical structure or in the extension of fundamental knowledge of organic reactions, his choice always lay in the direction of those researches which might directly or indirectly lead to the discovery of useful substances, especially in the field of medicine.

Pyman's grandfather, George Pyman, of Raithwaite Hall, Whitby, was a self-made man from the sea who eventually became the owner of a fleet of merchant vessels and in due course started shipping firms for his sons in several ports. George Pyman did much public work, becoming J.P. for Durham County, Councillor for the North Riding and Mayor of Hartlepool, and did much to develop the merchant shipping industry of Great Britain. Pyman's father, the fifth son of George, was a classicist who took honours at Cambridge—Trinity College—and subsequently read for the Bar, but abandoned this career in favour of a shipping business and a career in politics, at which he worked so hard that his health gave way in 1887. He acted as private secretary to Lord Rosebery; in 1892 he stood as candidate for Whitby in the Liberal interest. The disappointment of defeat caused a final break in his health, so that Frank Lee Pyman, then ten years of age, saw little of

his father thereafter. On his mother's side Pyman also inherited invaluable characteristics. His maternal grandfather, Henry Lee, who was at one time M.P. for Southampton, was head of the cotton firm Tootal, Broadhurst, and Lee. His daughter, Florence Lee, was Pyman's mother and on her fell the responsibility for the education of the family of six, of whom Frank Lee was the eldest, for her husband's illness developed into life-long disability. She was an exemplary mother, and Frank was ever ready to acknowledge his indebtedness for her influence during childhood and her advice in later life.

Pyman was born on April 8th, 1882, and received his schooling at Dover College. There he took a great liking to chemistry: his teacher, Pendlebury, encouraged him in adopting this as his career. At seventeen he went to Owens College, Manchester, gaining a James Gaskell Scholarship. There he came under the influence of W. H. Perkin, junior. Thus his inborn ability for practical science became directed to organic chemistry, in which he was later to achieve so much.

That he was an exceptional student is clear from the following account written by one of his contemporaries. "He was of a different class from most of us. We could see his ability from the first year and as time went on we realised that he was brilliant and an outstanding man, for on top of his ability to understand things more quickly than the rest of us, he was the hardest worker of the whole year.

"I think I have never seen a neater worker anywhere. His organic preparations were not made in large (and useless) quantities, but in test tubes. Everything was in apple-pie order on his desk, his note-book somehow escaped the stains and burnings which seemed the lot of us lesser men.

"And yet he was not a man aloof but a good mixer and a man whose company I always enjoyed. If I was in difficulties over some point I could not understand, Frank was always willing to help and explain most patiently. His unbounded enthusiasm for everything he took up was infectious. There seemed nothing he could not do and yet we never felt he despised us, nor did jealousy for his powers ever trouble us. If any rag was proposed, Frank would be in the thick of things."

These qualities of friendship continued with little change throughout his life and his rather breezy, frank and open way with his friends which was the basis of it was equally helpful to those who worked and those who played with him.

After graduating with first-class honours in 1902, he went to Zurich Polytechnic to study under Bamberger, with whom he engaged in research for which he was awarded a Ph.D. in 1904.

On his return to this country he spent a short period under T. E. Thorpe in the Government Laboratory. There he became dissatisfied through not finding opportunity to carry on research in organic chemistry, of which he had become enamoured and in 1906 he was appointed on the staff of Experimental Laboratories of the Wellcome Chemical Works, Dartford, and soon succeeded H. A. D. Jowett as head of the Department. During the next thirteen years he was engaged in research work on behalf of Burroughs Wellcome & Co., later succeeding F. B. Power as head of the Wellcome Research Laboratories in London. Thus he became interested in the application of chemistry to progress in therapeutics, to which the greater part of his experimental work was later devoted.

In 1919 he was appointed Professor of Technological Chemistry in the University of Manchester and in the Manchester College of Technology and for the next eight years he took a very active part in the academic life of Manchester.

At the College of Technology Pyman inherited a large staff, for the most part senior to him in age, length of service and technical knowledge, and with remarkable rapidity he succeeded in establishing the right influence and atmosphere to enable him to obtain for the University the best possible service from each of them. Professor F. M. Rowe, who at this time became his colleague, says of him: "It was Pyman's keenness for research and his ability for experimental work with his own hands, his desire to see all theoretical laboratory teaching at the highest possible standard and, above all, his businesslike ways which enabled him to knit his staff together so effectively. He had no use for a slacker, but once he was satisfied with the competence of a particular member of his staff, then he left that man very much to his own devices subsequently, although he was always available and ready to help if consulted.

"Pyman soon had a small laboratory equipped next to his private room and in it he settled down to his own work on glyoxaline derivatives, there being in it also space for one or two of the best graduates who elected to work under him on this subject. Pyman became extremely popular with all his really first-class students, but less so with the less well-prepared ones, who were not really ready, without further training, to succeed with preparative work in the glyoxaline series."

When the Fellowship of the Royal Society was conferred upon him in 1922 the students of the College insisted on forming a procession and taking him through the streets of Manchester in celebration.

In the year 1927 Pyman relinquished his Professorship in Manchester University in order to become Director of Research at the Nottingham Laboratories of Boots Pure Drug Co., the position he continued to hold until his death in 1944. There he gathered round him a group of research workers suited to his leadership; the department grew rapidly and a period of great activity followed.

Apart from publications made during the sixteen years which followed, Pyman was able to make substantial contributions to the development of manufacturing processes relating to arsphenamine, insulin, liver extract, saccharin and potassium permanganate.

In 1929 he was appointed a Director of Boots Pure Drug Company and took part in discussions on general commercial and industrial affairs. He was characteristically diffident about expressing an opinion if he felt

his knowledge did not justify him or if he considered the problem to be unsuitable for solution by the scientific method of approach. His gift of clear and concise expression inspired confidence and enabled him to put his views with great force.

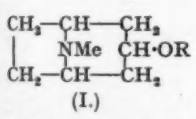
Pyman inaugurated regular monthly research conferences between selected academic workers in Chemistry, Biochemistry and Medicine and his scientific colleagues of Boots Pure Drug Co. He acted as chairman of this conference and thus most successfully assisted in the building of that bridge of understanding between academic and applied science for which so great a need exists.

In 1907 Pyman was married to Ida Catrine Lowry, daughter of George Lowry, and throughout the years that followed, in indirect ways she contributed greatly to his successful achievements. Pyman's home life was an especially happy one. The day's work finished and at week ends, he wanted nothing more than to be at home with his wife and family. One remembers how lustily he played with his children when they were young and how his interest in them in later life took precedence of everything else.

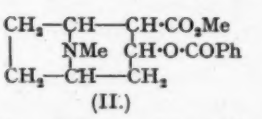
He played golf and billiards, but his chief recreation was that of gardening, at which he worked with great zeal. Moreover, his interest in horticultural science extended beyond his own garden, for the directing of Boots horticultural research became one of his many activities in later years. He paid many visits to other countries and these gave him and his wife great pleasure. They were both lovers of music and one of the few things that would draw him away from home was attendance at the opera, particularly when abroad. He also took great interest in orchestral gramophone music, Beethoven being his first choice.

Pyman's papers cover a considerable diversity of topics—essential oils, glucosides, alkaloids, glycerophosphates, organic compounds of arsenic, selenium amd bismuth, etc., but his work can be discussed as a contribution to three main subjects, which evoked his special interest.

His first paper, published with Jowett, started a series on the relation between chemical constitution and physiological action, which continued throughout his career. Jowett and Pyman began with a study of the tropeines (I), which are acyl esters of the amino-alcohol, tropine, the best known members of the group being the natural alkaloids, hyoscyamine and atropine, the *l*- and the *dl*-tropyl ester respectively. The useful tropeines are mydriatics, and as the effect of this action is readily observable in a roughly quantitative fashion, it was used to investigate the results of varying the acyl radical as indicated by R in (I).



(I.)



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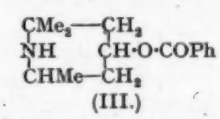

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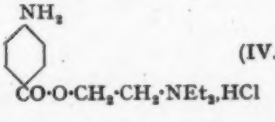


(IV.)

From this study Jowett and Pyman (J., 1909, **95**, 1020) were able to draw the following conclusions :— The current generalisation that a tropeine to have mydriatic properties must have (1) a benzene nucleus and (2) an aliphatic hydroxyl in the side chain containing the carboxyl group is not valid. The first postulate is approximately correct, but benzene may sometimes be replaced by pyridine, as in the moderately active β-2-pyridyl-α-hydroxypropionyltropeine.. The second postulate is incorrect and cases were found in which the hydroxyl group was nuclear, absent, replaced, or closed by lactone formation, without disappearance of mydriatic activity. It is valid to the extent that all the new tropeines tried and found at least as potent as homatropine, contained an alcoholic hydroxyl group.

From the tropeines it was a natural step to deal with local anæsthetics, since ecgonine, the basic nucleus of cocaine (II), is a tropinecarboxylic acid and tropacocaine, also a potent local anæsthetic, is the benzoic ester of ψ-tropine. Though cocaine is probably still the best all-round local anæsthetic, it has for many purposes been replaced by substitutes, which resemble it in being benzoyl esters of amino-alcohols. The skeleton :N·C·C·O·COR is common to most of the well-known local anæsthetics, *e.g.*, cocaine (II), β-eucaine (III), and novocaine (IV). Pyman prepared a series of compounds (V to IX) based on this skeleton (J., 1908, **93**, 1793) and a second series (X to XIII) of a more exploratory character (J., 1917, **91**, 167). Compounds (V) to (IX) all showed local anæsthetic activity, indicating that this skeletal structure has some influence in producing this property, but they were too toxic and irritant on injection to be of practical value. The second series (X to XIII) provided some striking contrasts. It was known that replacement of benzoyl by phenylacetyl in cocaine (II) led to loss of activity, whereas a similar change in α-eucaine has been stated to enhance the action. In this second series ethyl *p*-aminophenylacetate (X) proved inactive in contrast with ethyl *p*-aminobenzoate.

(V.) $Ph{\cdot}CO{\cdot}O[CH_2]_2{\cdot}NR{\cdot}[CH_2]_2{\cdot}O{\cdot}COPh$. R = Me, inactive : R = Et, just active.

(VI.) $Ph{\cdot}CO{\cdot}O{\cdot}CH(CH_2R){\cdot}CH_2{\cdot}O{\cdot}COPh$. R = NMe_2, NEt_2 or $C_5H_{10}N$, active.

(VII.) $C_5H_{10}N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COPh$. Slightly active.

(VIII.) $Ph{\cdot}CO{\cdot}O{\cdot}[CH_2]_2{\cdot}N\langle{}^{CH_2{\cdot}CH_2}_{CH_2{\cdot}CH_2}\rangle N{\cdot}[CH_2]_2{\cdot}O{\cdot}COPh$. Active.

(IX.) $NMe_2{\cdot}CH_2{\cdot}CHR{\cdot}O{\cdot}COPh$. R = piperonyl, active.

(X.) p-$NH_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO_2Et$. Inactive.

(XI.) p-$NH_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$. Inactive.

(XII.) $NEt_2{\cdot}CH_2{\cdot}CH(OR){\cdot}CH_2{\cdot}OPh$. R = H, active : R = COPh, too acid for test.

(XIII.) p-$NH_2{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}OEt$-$p$. Inactive.

Similarly (XI), which is " novocaine " (IV) with its *p*-aminobenzoic acid group replaced by a *p*-aminophenylacetic residue, is inactive. In (XII) it was hoped to test the effect of replacing one benzoyl group of (VI) by a phenyl group. The benzoate (XII, R = COPh) was too acid for test, but the alcohol (XII, R = H) was active.

The dystherapeutic effect of a slight change in the acyl radical in these local anæsthetics is in strong contrast to the behaviour of the tropeines, where, as Jowett and Pyman found, the tropyl group may be replaced by acids ranging from phenylacetyl to phthalidecarboxyl and β-2-pyridyl-α-hydroxypropionyl without disappearance of mydriatic activity.

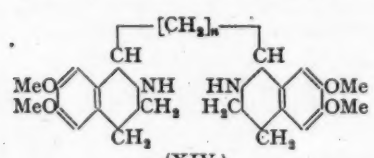
At this period there was a disposition on the part of chemists to believe that similarity in chemical structure implied similarity in pharmacological action. It is now known that, though this simple relation between chemical structure and pharmacological action may be shown over a limited range, *e.g.*, in a homologous series of compounds, it is not generally valid and other factors, physical and biological, are at least as important as the molecular architecture. Pyman's early work on this subject contributed materially to realisation of the complexity of the factors involved in attempts to synthesise substances having a required pharmacological action and his later papers illustrate the development of these ideas. Thus, in his paper (with E. C. S. Jones; J., **1925**, **127**, 2588) on pungency in acid amides of the capsaicin (decenovanillylamide) type, he states, amid conclusions relating to variation in structure, that the shape of the side chain, rather than its weight, determines the degree of pungency.

The paper on " The Variation of Phenol Coefficients in Homologous Series of Phenols " (with C. E. Coulthard and J. Marshall; J., 1930, 280) involves biological conditions of a simple type and, as might be expected, the results are free from the kind of contrast referred to above. Using the series of alkyl side chains from methyl to *n*-heptyl in phenol, the three cresols and guaiacol, it is shown that in each series the phenol coefficient rises to a maximum at the *n*-amyl derivative, and then falls, the highest figure being given by 5-*n*-amyl-*o*-cresol. Mention must also be made of the work on amidines of pharmacological interest (with A. P. T. Easson; J., 1931, 2991), in which stress is laid on the structural similarity of the amidine group, $\cdot C(:NH)\cdot NH_2$, to the carboxyl group and to the solubility of amidine bases in both water and immiscible solvents. On these grounds it was considered worth while to try replacement of the carbethoxy-group by the amidine group for local anæsthetic action. *p*-Aminobenzamidine was inactive as compared with ethyl *p*-aminobenzoate, but *p*-carbethoxybenzamidine, $CO_2Et\cdot C_6H_4\cdot C(:NH)\cdot NH_2$, was slightly active and benzenylveratrylamidine, $NH_2\cdot CPh{:}N\cdot C_6H_3(OMe)_2$, showed well-marked activity.

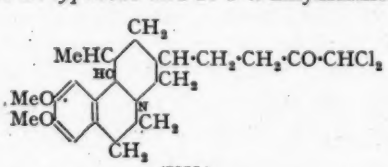
Various amidines were also tried biologically in other directions; they were weak antiseptics, had no well-defined action as hypoglycæmic drugs and were inactive in canary malaria, but one at least, *p*-hydroxyphenylacetamidine, $HO\cdot C_6H_4\cdot CH_2\cdot C(:NH)\cdot NH_2$, like its relative *p*-hydroxyphenylethylamine, showed pressor action, which disappeared in its *N*-methyl derivative.

Probably the most interesting of all Pyman's contributions to this subject was described in his presidential address to the chemical section of the British Association in 1937 (*J. Soc. Chem. Ind.*, 1937, **56**, 789). It arose out of his important work on emetine, which is referred to later. Emetine is used in medicine as a remedy for amœbic dysentery and in the hope of finding a synthetic substitute he devised a method of preparing substances of the type represented by (XIV; cf. emetine). Six of these products were made (Child and Pyman, J., 1929, 2010) and tested as amœbicides and anti-malarials and found inactive. Attention was next directed (Child and Pyman, J., 1931, 36) to a series suggested by the amœbicidal activity (Pyman and Wenyon, *J. Pharm. Exp. Ther.*, 1917, **10**, 237) of a substance, $C_{20}H_{27}O_3NCl_2$, derived from cephaeline and for which Brindley and Pyman (J., 1927, 1067) had proposed formula (XV), which retains the reduced benzpyridocoline nucleus of the emetine formula (XXXII). Typical examples of the compounds synthesised are (XVI*a*) and (XVI*b*). Of the eight substances tested, the most active was (XVI*b*), which inhibited the growth of *Entamœba histolytica* in cultures at 1 in 25,000 compared with emetine, which was effective at 1 in 500,000.

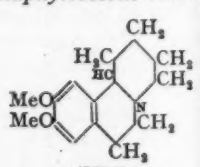
Attention was next given to the alkaloids harmine and harmaline, which had acquired an undeserved reputation as anti-malarials. These were demethylated and from the resulting phenolic bases, harmol and harmalol, homologous series of alkyl ethers (XVII; harmol ethers, R = alkyl) were prepared and submitted to biological tests. They were inactive in bird malaria, and were not trypanocidal, but there was a peak of anti-bacterial activity at *O*-*n*-butylharmol for *B. typhosus* and at *O*-*n*-amylharmol for *Staphylococcus aureus*.



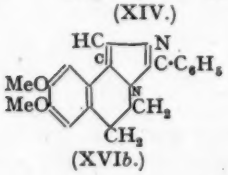
(XIV.)



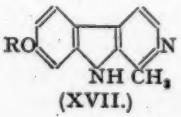
(XV.)



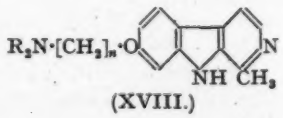
(XVI*a*.)



(XVI*b*.)



(XVII.)

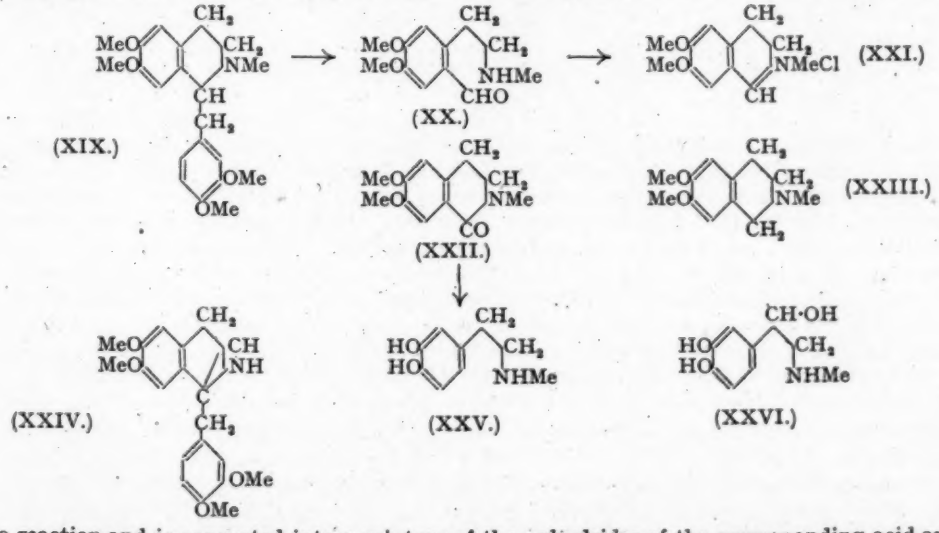


(XVIII.)

Maximum amœbicidal activity was reached at *O*-*n*-nonylharmol for the alkyl ethers (with Coulthard and Levene, *Biochem. J.*, **1933**, **27**, 727; cf. Coulthard, *ibid.*, **1934**, **28**, 264), but as this substance had the undesirable property of yielding sparingly soluble salts, a solubilising component was introduced in place of a simple alkyl group and a new homologous series of compounds represented by (XVIII) was made, the size of R (the *N*-alkyl group) and of *n* being varied. In this series the peak of amœbicidal activity was reached at *O*-λ-di-*n*-butylaminoundecylharmol (1 in 750,000 to 1 in 4,000,000) compared with *O*-*n*-nonylharmol at (1 in 200,000 to 1 in 500,000) and emetine (1 in 2,000,000 to 1 in 10,000,000). These results indicated that in the development of amœbicidal action in this series the side chain was more important than the harmol nucleus. Preliminary experiments showed that the attachment of the chain $(C_4H_9)_2N\cdot[CH_2]_{10}\cdot$ to a simple substituted amino-group seemed to give high amœbicidal efficiency. A series of substances of the type $NRR'\cdot[CH_2]_n\cdot NRR'$ was prepared and trials of this group of compounds indicated a peak of activity (1 in 3,000,000) at ακ-tetra-*n*-amyldiaminodecane and no variants on this gave higher efficiency.

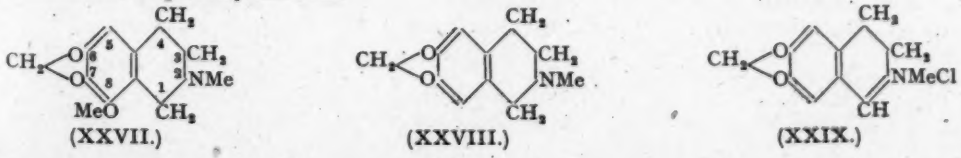
iso*Quinoline Alkaloids*.—In 1909 Pyman showed that, just as narcotine and hydrastine undergo hydrolytic oxidation to cotarnine and hydrastinine respectively, so laudanosine (XIX; *N*-methyl-1 : 2 : 3 : 4-tetrahydropapaverine) can be converted into 4 : 5-dimethoxy-2-β-methylaminoethylbenzaldehyde (XX) (J., 1909, **95**, 1266), which in the form of its salt, 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium chloride (XXI), came into medical use as a uterine styptic.

Extension of this investigation to other substituted tetrahydro*iso*quinolines led to the conclusion that, whereas 1-alkyl derivatives do not react in this way, 1-benzyl, 1-benzyl-2-alkyl and 1-benzyl-2-acyl derivatives can undergo this simultaneous oxidation and scission (J., 1909, **95**, 1738). This investigation included work [*ibid.*, p. 1610; (with Reynolds), J., 1910, **97**, 1320; 1915, **107**, 176] on the reduction products of papaverine. Pyman cleared up the existing confusion and found that in addition to tetrahydropapaverine, there was formed an anomalous product, pavine, at first believed to be 1 : 2-dihydropapaverine, but which was eventually shown by a study of its exhaustive methylation products to have a bridged-ring structure as in (XXIV). When 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium chloride (XXI) is boiled with alkali, it undergoes a



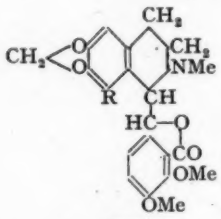
Cannizzaro reaction and is converted into a mixture of the anhydrides of the corresponding acid and alcohol, *viz.*, 1-keto-6 : 7-dimethoxy-2-methyltetrahydro*iso*quinoline (XXII) and 6 : 7-dimethoxy-2-methyltetrahydro*iso*quinoline (XXIII). The former can be hydrolysed, undergoing demethylation of both methoxyl groups and hydration of the lactam group, yielding 3 : 4-dihydroxyphenylethylmethylamine (XXV) a substance qualitatively resembling adrenaline (XXVI) in pharmacological action (J., 1910, **97**, 264).

Continuing work on *iso*quinoline alkaloids, Pyman and Remfry (J., 1912, **101**, 1595) accomplished the conversion of cotarnine into hydrastinine. The former was reduced to hydrocotarnine (XXVII), and the methoxyl group of the latter eliminated by the action of sodium in fusel oil to yield hydrohydrastinine (XXVIII), which was oxidised to hydrastinine (XXIX; as chloride). In this reaction four interesting phenolic bases are also formed in small quantity by the following replacements: CH_2O_2: at 6 and 7 into OH at 6 or 7 and H at 7 or 6, with or without the substitution of H at 8 for MeO (see XXVII). Up to that time, hydrastinine had been made from the costly alkaloid hydrastine and this new procedure made the relatively cheap opium alkaloid, narcotine, available as the primary material.

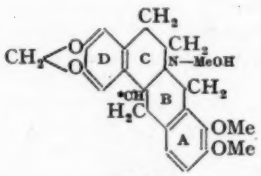


In 1931 Pyman was associated with Hope, Remfry, and Robinson (J., 1931, 236) in a synthesis of hydrastine (XXX, R = H) which had features of special interest. This alkaloid has two asymmetric carbon atoms and two *dl*-forms (*a*) and (*b*) were obtained. In a subsequent paper (J., 1934, 1315) dealing with the stereoisomerides of narcotine (XXX, R = OMe) and hydrastine (XXX, R = H) it was shown that the natural forms, *l*-narcotine and *l*-hydrastine, are each converted by hot methyl-alcoholic potassium hydroxide into a mixture of the original alkaloid and a new, optically active isomeride, due to partial racemisation at one asymmetric carbon atom, presumably that of the " phthalide " nucleus. In the case of narcotine, the new isomeride, *l*-β-narcotine, is of lower lævorotation than natural, *l*-α-narcotine, whilst in the case of hydrastine the new form is of higher lævorotation. Hydrastine is therefore considered to differ from natural narcotine in stereochemical configuration and to be *l*-β-hydrastine, the new form being *l*-α-hydrastine. On this basis the complete synthesis of the natural form of hydrastine will probably involve the resolution of hydrastine-*b*, which should yield *l*-α-hydrastine, and it was shown that the latter can be epimerised in minute amount by hot methyl-alcoholic potassium hydroxide.

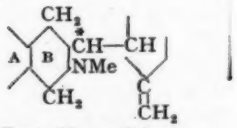
Pyman's work on berberine and its derivatives began with an account of the oxidation of berberine-acetone to the phenol-betaine *neo*oxyberberine (J., 1911, **99**, 1690). Somewhat later he investigated with Jowett (J., 1913, **103**, 290) the bark of *Xanthoxylum brachyacanthum*, F. Muell., and showed that it contained γ-homochelidonine in small amount, and in much larger proportion a second alkaloid, which was isolated in the form of its chloride and shown to be *l*-α-tetrahydroberberine (canadine) methochloride (XXXI with OH → Cl). This led to a study (J., 1913, **103**, 817) of the two forms, α- and β-, of the methochloride.



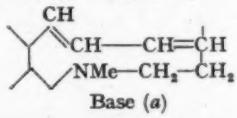
(XXX.)



(XXXI.)



Base (*b*) = *dl*-form
Base (*c*) = *l*-form



Base (*a*)

Both caused paralysis of voluntary muscle, similar to that produced by curare, but the two provided another instance of the influence of configuration on pharmacological action, the α-form being only one-tenth as active as the β-form. Out of this work arose the completion (J., 1913, **103**, 817) of the work done by Voss and Gadamer (*Arch. Pharm.*, 1910, **248**, 43; cf. McDavid, Perkin, and Robinson, J., 1912, **101**, 1218) in explaining the reactions occurring when the tetrahydroberberine alkylhydroxides are heated. Pyman showed that three anhydro-bases can be formed and that their relative proportions depend on the experimental conditions and on the configuration of the starting material. Thus he found that while the *dl*-form of tetrahydroberberine methohydroxide (XXXI) gave rise to two anhydro-bases (*a*) and (*b*), the *l*-form gave an optically active form (*c*) in addition to (*a*) and (*b*), the yield of base (*a*) being the same in both cases, while that of (*b*) in the first case is about equal to that of (*b*) + (*c*) from the *l*-form, indicating that (*b*) is the racemic form of (*c*). Under certain experimental conditions base (*a*) is not found in the reaction products, owing to the fact that it is unstable under these conditions and is converted into the *dl*-methohydroxide (XXXI), which then yields the *dl*-anhydro-base (*b*). The course of the reactions was represented thus :

l-Canadine methohydroxide ⟶ Base (*a*) ⇄ *dl*-Tetrahydroberberine methohydroxide
↓ ↓
Base (*c*) Base (*b*)

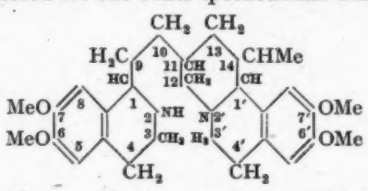
The culminating point in Pyman's work on *iso*quinoline alkaloids is that on the ipecacuanha bases, which was begun with Carr (J., 1914, **105**, 1591) in order to clarify the then somewhat confused chemistry of this drug, which just previously had been successfully used in cases of amœbic dysentery. The work was continued by Pyman until 1927 [J., 1917, **111**, 419; 1918, **113**, 222; (with Brindley), J., 1927, 1067]. The three known ipecacuanha alkaloids, emetine, cephaeline and psychotrine, were first prepared, carefully purified and characterised, new empirical formulæ assigned to them, and their inter-relationships established. For the first time, clear evidence that they belonged to the *iso*quinoline group of alkaloids was provided by the isolation of 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid from the oxidation of emetine by permanganate. In 1917 two new alkaloids were isolated from the drug, of which one, emetamine, could not at once be related to any of the three already known. The second proved to be psychotrine methyl ether and the following interconversions were effected :

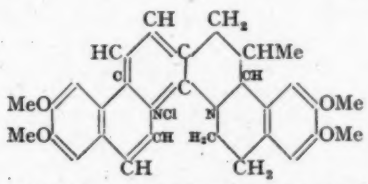
Cephaeline $C_{25}H_{28}N_2(OMe)_3OH$	←	Psychotrine $C_{25}H_{26}N_2(OMe)_3OH$	→	*iso*Cephaeline $C_{25}H_{28}N_2(OMe)_3OH$
↓		↓		↓
Emetine $C_{25}H_{28}N_2(OMe)_4$	←	*O*-Methylpsychotrine $C_{25}H_{26}N_2(OMe)_4$	→	*iso*Emetine $C_{25}H_{28}N_2(OMe)_4$

Some progress had also been made with the Hofmann degradation of emetine and in the determination of characteristics bearing on the constitution of all five alkaloids.

In 1927, Späth and Leithe provided evidence of the existence of a second *iso*quinoline nucleus in emetine and, on that basis, suggested a partial formula for this alkaloid. This led Pyman to publish a formula for emetine, which Sir Robert Robinson had suggested two years previously, based on a theory of structural or genetic relationships among the *iso*quinoline alkaloids. This formula was modified slightly by the transfer of a methyl group from C_{12} to C_{14} (XXXII), mainly to account for the oxidation of emetine, *iso*emetine or *O*-methylpsychotrine to the deep-red substance, rubremetinium chloride (XXXIII), in the formation of which eight hydrogen atoms are lost from emetine and one of the nitrogen atoms becomes quaternary, while the other ceases to show basic properties assumed to be due to amidine formation. Formulæ, based on that of emetine, were also suggested for the other ipecacuanha alkaloids.

(XXXII.)





(XXXIII.)

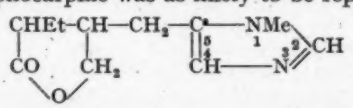
Mention has been made already of the work on synthetic amœbicidal drugs, suggested by this investigation of emetine and its associates.

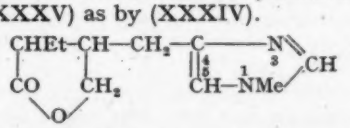
Other Alkaloids.—Pyman also published a number of papers on other alkaloids, notably conessine and holarrhenine (J., 1919, **115**, 163) derived from *Holarrhena congolensis*, a drug which was alleged to exert a local anæsthetic action and is still of some interest as a not very satisfactory remedy for amœbic dysentery. He also isolated and characterised a series of three alkaloids from the Australian plant *Daphnandra micrantha* (J., 1914, **105**, 1679).

Most of the *Datura* species examined up to 1908 had been found to contain one or more of the usual solanaceous alkaloids, atropine, hyoscyamine or hyoscine and Pyman and Reynolds (J., 1908, **93**, 2077) in their discovery of meteloidine in *Datura meteloides* found a solanaceous alkaloid of a new type, in which the basic nucleus tropine was replaced by teloidine, which King (J., 1919, **115**, 487) has suggested is probably a trihydroxytropane, and the typical esterifying acid, tropic or benzoic, was replaced by tiglic acid.

Pilocarpine and Glyoxaline.—The subject which probably interested Pyman more than any other, *viz.*, the chemistry of glyoxaline, also arose primarily from an alkaloidal investigation. In the years 1900 to 1903, thanks to the work of Jowett in this country and Pinner in Germany, Pinner and Schwarz were able to suggest a formula (XXXIV) for pilocarpine. Jowett confirmed this suggestion by the isolation of a series of dialkylglyoxalines from the products of distillation with soda-lime of *iso*pilocarpine, a stereoisomeride of pilocarpine, though he pointed out that these dialkylglyoxalines might be either 1 : 4- or 1 : 5-dialkyl derivatives, and that consequently pilocarpine was as likely to be represented by (XXXV) as by (XXXIV).

(XXXIV.)

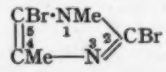


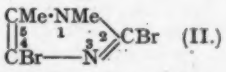


(XXXV.)

That the 1 : 5-formula (XXXIV) was probably correct was indicated by Pyman (J., 1910, **97**, 1814) from a study of the two dimethylglyoxalines produced by the methylation of 4 (or 5)-methylglyoxaline. The latter, like all glyoxalines containing a free imino-hydrogen atom, shows virtual tautomerism between positions 4 and 5, whence the two dimethylglyoxalines must be the 1 : 4- and 1 : 5-forms. The one having b. p. 224—225° was identical with the substance obtained from *iso*pilocarpine. Both yielded dibromo-compounds, which must be represented thus :

(I.)

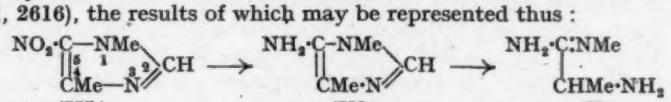




(II.)

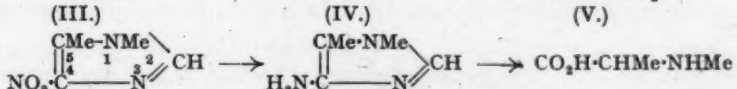
Pyman found by a simple distribution method that one of these dibromo-compounds was a weaker base than the other, which he explained as due to the proximity of the bromine atoms at C_2 and C_4 to the basic N at position 3 as in (II) and since the weaker base is the derivative of the dimethylglyoxaline from *iso*pilocarpine, it was assumed that the latter, and therefore pilocarpine also, yielded 1 : 5-dimethylglyoxaline. This assumption was proved correct in Pyman's later work on the reduction of the nitro-derivatives of the two dimethylglyoxalines (J., 1922, **121**, 2616), the results of which may be represented thus :

A.



(III.) (IV.) (V.)

B.

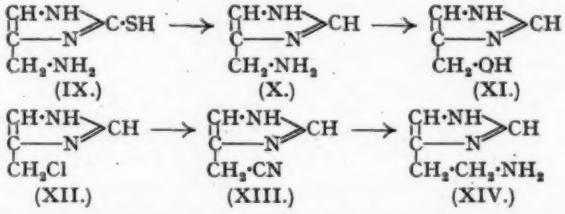


(VI.) (VII.) (VIII.)

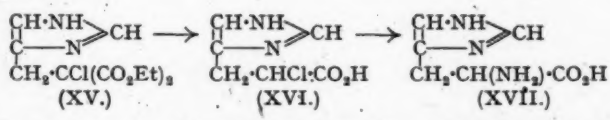
The identity of (V) as *dl*-alanine-*N*-methylamidine was established by its hydrolysis to *dl*-alanine, ammonia and methylamine, which also accompany it in the primary reaction. Similarly *dl*-*N*-methylalanine (VIII) in operation B is accompanied by ammonia.

Pyman also added the new alkaloid pilosine to the jaborandi series (J., 1912, **101**, 2261). It is decomposed by boiling with alkali into benzaldehyde and a new alkaloid, pilosinine, which closely resembles pilocarpine and *iso*pilocarpine in physical and chemical properties and in pharmacological action, and is regarded as a lower homologue of this pair, corresponding stereochemically with *iso*pilocarpine. The parent alkaloid pilosine is represented by the formula for pilocarpine (XXXIV) with the ethyl group replaced by $C_6H_5{\cdot}CH{\cdot}OH$.

While this orientation of substituents in the glyoxaline nucleus was proceeding, another natural product with the same nucleus began to attract interest, *viz.*, histamine (4-β-aminoethylglyoxaline), a substance with potent pharmacological action, whose occurrence in ergot extracts had been discovered by Barger and Dale (J., 1910, **97**, 2592). Its preparation from histidine was improved (with Ewins, J., 1911, **99**, 339) and processes for the synthesis of it and a number of its homologues devised (J., 1911, **99**, 668, 2172; with Fargher, J., 1921, **119**, 734; with Garforth, J., 1935, 489), of which the first may be mentioned. 2-Thiol-4-aminomethylglyoxaline (IX) on oxidation by nitric acid yielded, instead of the expected aminomethylglyoxaline (X), 4-hydroxymethylglyoxaline (XI). The hydroxyl group in the latter was replaced by chlorine, and the 4-chloromethylglyoxaline (XII) treated with potassium cyanide to give 4-cyanomethylglyoxaline (XIII), which was then reduced by sodium in alcohol to the required base, 4-β-aminoethylglyoxaline (XIV).



4-Chloromethylglyoxaline (XII) proved to be a reactive substance and Pyman was able to use it to synthesise substances structurally allied to pilocarpine (J., 1912, **101**, 530) and for his well-known synthesis of histidine (J., 1911, **99**, 1386). For the latter purpose it was condensed with ethyl sodiochloromalonate to give ethyl 4-glyoxalinemethylchloromalonate (XV), which was hydrolysed and partially decarboxylated to *dl*-α-chloro-β-glyoxaline-4-propionic acid (XVI). This, when heated with concentrated aqueous ammonia at 110°, yielded *dl*-histidine (XVII), which was resolved by fractional crystallisation of the acid tartrate to yield *l*-histidine identical with the natural product.



A second synthesis starting from glyoxaline formaldehyde was published later (J., 1916, **109**, 186).

In 1919 Pyman began a more academic study of reaction and substitution in the glyoxaline nucleus and this was continued and developed after his professorial appointment at Manchester. It included particularly an investigation of the bromination of glyoxaline and the 1-, 2- and 4-methylglyoxalines (with Balaban, J., 1922, **121**, 947; 1924, **125**, 1564; Light, J., 1922, **121**, 2626; Timmis, J., 1923, **123**, 494), the direct sulphonation of glyoxaline, 2-methylglyoxaline, and its 4-bromo-derivative, and 4(5)-methylglyoxaline (with Ravald, J., 1920, **117**, 1429; Forsyth and Moore, J., 1924, **125**, 919; Barnes, J., 1927, 2711); the nitro- and related derivatives of glyoxaline and its alkyl and aryl compounds (with Fargher, J., 1919, **115**, 217, 1015; Grant, J., 1921, **119**, 1893; Stanley, J., 1924, **125**, 2484; Bhagwat, J., 1925, **127**, 1832; Forsyth and Numkar, J., 1926, 800, 2912: 1930, 397; Bryans, J., 1929, 549) and probably most important of all, the series of seven papers on the tautomerism of amidines inspired, no doubt, by his successful solution of the pilocarpine alkyl orientation problem already referred to, and concerned first with alkylation in the nitro- and aryl-glyoxalines and eventually extended to the alkylation of open-chain amidines, arylamidines and pyrimidines (J., 1923, **123**, 361, 367, 3359; with Hazeldine and Winchester, J., 1924, **125**, 1431; Forsyth, J., 1925, **127**, 573; 1926, 2502; Chew, 1927, 2318).

The need for brevity imposed by present conditions makes it impossible to summarise the knowledge thus gained of the chemistry of this interesting and biologically important heterocyclic nucleus.

For the same reason the foregoing account has had to be restricted to the three principal types of investigation which interested Pyman. They at least serve to indicate the importance of his contribution to the progress of our science, which he served so devotedly throughout his life. Pyman will be remembered not only as a chemist of outstanding gifts but as a man upright in all he did and of unswerving loyalty to his friends and colleagues.

FRANCIS H. CARR.
T. A. HENRY.

GEORGE STALLARD.

1854—1944.

GEORGE STALLARD, who died on April 5th, 1944, was one of the oldest Fellows of the Chemical Society, having been elected in December, 1879. He was the *doyen* of Science Masters in public schools, having held appointments at St. Paul's and Rugby, where he organised the teaching of chemistry on modern lines with strong emphasis on laboratory work.

He was born on July 6th, 1854, the son of Mr. George Stallard of Havant, the owner of a parchment factory. He was educated at Hurstpierpoint College and proceeded with a scholarship to Keble College, Oxford, whence in 1876 he took an Honours Degree (first class) in Natural Science, with chemistry as his principal subject.

As there was no chemical teaching at Keble College, Stallard went for lectures and laboratory work to the University Chemical Department at the Museum. Odling was then the Professor, and W. W. Fisher and John Watts superintended the laboratory work. Stallard found Watts a well-informed and painstaking teacher and was fortunate in securing him as his private tutor. Stallard always acknowledged his great indebtedness to Watts.

After taking his degree, Stallard was appointed Science Master at the Bedford County School at Elstow, which had adopted a modern curriculum but where Stallard had to teach several subjects besides chemistry. From there in 1878 he went to St. Paul's, then in the City, as its first Science Master, although still having also to teach other subjects than chemistry. F. W. Walker was Headmaster and was not credited with much enthusiasm for science teaching. He began by giving Stallard the option of teaching some other subject than chemistry. Stallard preferred to adhere to chemical teaching and Walker, evidently impressed by his sincerity, afterwards gave him every encouragement, so that Stallard looked back on his five years at St. Paul's as the happiest time in his school life.

His first pupil was a new boy who desired to take up chemistry and who had not been changed by Walker's advocacy of other subjects. He came with the boy to Stallard's room and said, " I hand over this boy to your care, body and soul." That boy was my brother, the late Professor M. J. R. Dunstan, who from St. Paul's gained a Postmastership at Merton College, Oxford, took an Honours Degree in Chemistry, and became successively Principal of the Wye Agricultural College and the Cirencester Agricultural College.

On going to Rugby in 1883, Stallard found Jex-Blake as Headmaster and again in addition to chemistry was required to teach other subjects. There was then no proper laboratory. In 1887, Percival succeeded Jex-Blake. He came from Clifton, where Tilden had made great headway in the teaching of chemistry. Stallard was now able to devote himself entirely to chemistry and, although there was no adequate laboratory until 1905, he continued to make chemistry of increasing interest to the boys, with whom he had some conspicuous successes. Among these were Nevil Sidgwick, now Professor at Oxford, and Sir Will Spens, Vice-Chancellor and Master of Corpus Christi College, Cambridge.

Stallard soon acquired great influence in the school. In 1893 he became a House Master, built Tudor House, and firmly established chemistry in the school curriculum, largely owing to the improvements he made in laboratory teaching. He took immense trouble in teaching both the ordinary boys and those whom he was preparing for scholarship examinations. He retired in 1913.

In 1887, the British Association appointed a Committee to report on the teaching of chemistry in schools, of which Dr. W. J. Russell was chairman and I was secretary. Stallard was one of the members and with Francis Jones (Manchester), Dunn (Bath), and Shenstone (Clifton), took an active part in the proceedings.

Above all Stallard was a schoolmaster but with many other interests. He was interested in art, was well read in English literature, was a good linguist, was active in sport, and while at Rugby was often to be seen in the hunting field and at the rifle range. He was also a keen mountaineer, and spent several vacations climbing in the Dauphiné, where later he built a Chalet. Here he hunted chamois and in Sardinia moufflon.

He died within a short time of his wife, his devoted companion, who will also be remembered as the good friend of many generations of schoolboys.

WYNDHAM R. DUNSTAN.

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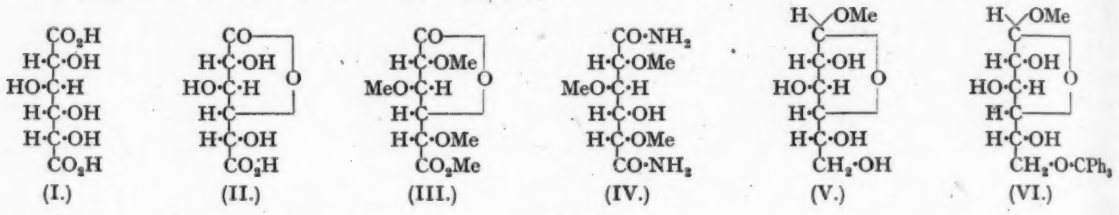
154. *Lactones of Glucosaccharic Acid. Part II.* 2 : 3 : 5- *and* 2 : 4 : 5-*Trimethyl Glucosaccharolactone.*

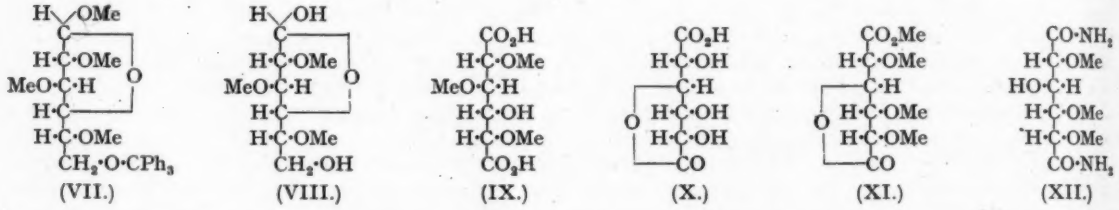
By F. SMITH.

The saccharolactone obtained by Sohst and Tollens from glucose by oxidation with nitric acid is shown to be a mixture of glucosaccharo-3 : 6- (X) and -1 : 4-lactone (II). This follows from the methylation of the mixture which affords 2 : 4 : 5-*trimethyl glucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (XI) and 2 : 3 : 5-*trimethyl glucosaccharo*-1 : 4-*lactone* 6-*methyl ester* (III). Both these substances have been identified, and the latter has been synthesised from glucose.

OXIDATION of glucose or starch with nitric acid affords glucosaccharic acid (I), which can be readily isolated in the form of its acid potassium salt. This salt can be converted into a calcium salt, which upon treatment with oxalic acid yields (in solution) saccharic acid. Evaporation of the solvent from such a solution of saccharic

acid gives a syrup which slowly crystallises. Recrystallisation of this product from ether gives the so-called "saccharolactone" (Sohst and Tollens, *Annalen*, **1888**, **245**, 1, 19). Potassium hydrogen saccharate can, however, be converted directly into "saccharolactone" by addition of sulphuric acid, followed by elimination of potassium sulphate. This "saccharolactone" was thought to be glucosaccharo-3 : 6-lactone (X) (Rehorst and Scholz, *Ber.*, **1936**, **69**, 524), but the work herein described proves that it is a mixture of (X) and glucosaccharo-1 : 4-lactone (II). This conclusion has been reached as a result of the observation that among the products of the methylation of Sohst and Tollens's saccharolactone (m. p. 133°) with silver oxide and methyl iodide there have been found 2 : 3 : 5-*trimethyl glucosaccharo*-1 : 4-*lactone* 6-*methyl ester* (III) and 2 : 4 : 5-*trimethyl glucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (XI).





The crystalline ester (III) was identified by the following experimental facts. Analysis showed that it had the formula $C_{10}H_{16}O_7$ and contained four methoxyl groups. The presence of a carbomethoxy-group in (III) was proved by the fact that upon treatment with sodium hydroxide one methoxyl group was eliminated. Moreover, during this saponification 2 equivs. of alkali were consumed, and hence the existence of a lactone ring was indicated. The presence of an ester methoxyl group and a lactone ring in the ester (III) was confirmed by the observation that treatment of the latter with methyl-alcoholic ammonia effected removal of one methoxyl group and formation of the crystalline *diamide* (IV) of a trimethyl saccharic acid. This diamide showed a negative Weerman test for α-hydroxy-amides (*Rec. Trav. chim.*, **1917**, **36**, 16). Hence both hydroxyl groups at C_2 and C_5 must be blocked by methyl residues. The location of two of the methyl groups at C_2 and C_5 was supported by the observation that vigorous treatment of (III) with nitric acid caused no breakdown of the chain of six carbon atoms. It was thus evident that the third methyl group must be in either position 3 or 4, in which case (III) is either the 2 : 3 : 5- or the 2 : 4 : 5-trimethyl derivative of saccharic acid. The former view was proved to be correct by the synthesis of 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester as follows: Treatment of glucose with 1% methyl-alcoholic hydrogen chloride gave methylglucofuranoside (V), and when this was allowed to react with trityl chloride, 6-*trityl methylglucofuranoside* (VI) was produced. Methylation of (VI) first with methyl sulphate and sodium hydroxide and then with silver oxide and methyl iodide yielded 6-*trityl* 2 : 3 : 5-*trimethyl methylglucofuranoside* (VII). The trityl group in this substance was easily removed by means of ethereal hydrogen chloride, giving 2 : 3 : 5-*trimethyl methylglucofuranoside*, from which 2 : 3 : 5-*trimethyl glucose* (VIII) was readily obtained by hydrolysis with dilute sulphuric acid. Oxidation of either (VIII) or its methylglucoside with nitric acid transformed both the reducing group at C_1 and the primary alcoholic group at C_6 into carboxyl groups, and there resulted 2 : 3 : 5-trimethyl saccharic acid (IX). Esterification of the latter followed by distillation gave rise to crystalline 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester. This and its diamide proved to be identical respectively with the ester (III) and the diamide (IV) derived from the so-called saccharolactone.

The structure (XI) assigned to the second trimethyl glucosaccharolactone methyl ester is based upon the fact that the crystalline *diamide* (XII) obtained from (XI) by means of methyl-alcoholic ammonia gave a negative Weerman test, thus proving that both the hydroxyl groups at C_2 and C_5 are substituted with methyl residues. The ester lactone (XI) must therefore be either a 2 : 3 : 5- or a 2 : 4 : 5-trimethyl derivative. The diamide now under discussion, however, was different from the foregoing diamide (IV), and hence this second trimethyl glucosaccharolactone methyl ester must be the 2 : 4 : 5-trimethyl derivative (XI).

The identification of the two trimethylglucosaccharolactone methyl esters (III) and (XI) demonstrates that Sohst and Tollens's saccharolactone is a mixture of the 3 : 6- (X) and the 1 : 4-lactone (II).

In addition to the formation of the two trimethyl saccharolactone methyl esters (III) and (XI), the methylation of the so-called saccharolactone also afforded 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (Smith, J., this vol., p. 513), methyl oxalate, and methyl dimethoxyerythrosuccinate. The formation of the last two susbstances probably results by oxidative cleavage of the six-carbon chain between C_2 and C_3 by the agency of the silver oxide, but which substance undergoes this breakdown is not clear.

Experimental.

Fractional Distillation of Syrup obtained by Methylation of Saccharolactone with Silver Oxide and Methyl Iodide.—Saccharolactone (m. p. 133°) was subjected to methylation with silver oxide and methyl iodide in the presence of acetone according to the conditions previously given (Smith, this vol., p. 514). After each methylation the excess of solvent was distilled off by heating the reaction mixture on the water-bath. Towards the end of the operation a crystalline sublimate was detected in the condenser. This was removed mechanically, and shown to be methyl oxalate by m. p. and mixed m. p. 53°, and by the fact that a solution of it gave a white precipitate (insoluble in acetic acid) when treated with calcium chloride solution. The crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester was separated and had m. p. and mixed m. p. 89°. Removal of solvent from the mother-liquors accumulated from several preparations gave a pale yellow liquid which was subjected to fractional distillation from a Widmer flask: the following fractions were obtained.

Fraction.	OMe, %.	Ester OMe,* %.	Wt., g.	B. p./0·02 mm. (bath temp.).	$n_D^{17°}$.	$[\alpha]_D$ in H_2O.	Equiv.†
I	58·5	30·3	1·1	115—125°	1·4340—1·4390	+21°	105
II	54·6	23·4	1·8	135—140	1·4610—1·4630	+10	115
III	53·0	19·6	3·73	135—140	1·4630	+ 6	120
IV	50·0	17·3	3·33	140—150	1·4630—1·4640	+25	114
V	45·9	14·8	1·7	150—165	1·4660—1·4675	+47	119
VI	45·6	18·4	1·2	>165	1·4720	+45	108

* The ester methoxyl content was determined by heating 10—20 mg. of the fraction with 0·3N-barium hydroxide (3 c.c.) for 1 hour at 60°. Excess barium hydroxide was neutralised by passing carbon dioxide over the surface of the liquid, which was shaken. The excess of solvent was removed by heating the mixture in a current of dry air, and any final traces were eliminated by heating in a vacuum for 30 minutes at 70—80°. These operations were performed in a semimicro-Zeisel apparatus and a methoxyl determination was carried out upon the residue consisting of the barium salt of the organic acid and barium carbonate. The ester methoxyl value was obtained by subtracting the methoxyl value obtained by this operation from that of the original fraction.

† The equivalent weight was determined by heating 10—20 mg. of the fraction with 0·02N-sodium hydroxide (10 c.c.) for 1½ hours at 55°, care being taken to prevent ingress of carbon dioxide from the air. The solution was then cooled, and the amount of sodium hydroxide required for hydrolysis determined by titration of the excess with 0·02N-sulphuric acid. A blank experiment was carried out simultaneously.

Identification of Methyl Dimethoxyerythrosuccinate (*Methyl Dimethyl* meso*Tartrate*).—Fraction (I) crystallised spontaneously, and the crystals were separated by tiling a portion; they then had m. p. 63—67°. The main bulk of the fraction was triturated with light petroleum–ether, and the crystals were washed by decantation with the same mixed solvent. Two crystallisations from ether gave methyl dimethoxyerythrosuccinate, m.p. 68°; this ester was optically inactive in methyl alcohol (*c*, 1·5) (Found: OMe, 60·1. Calc. for $C_8H_{14}O_6$: OMe, 60·1%). Treatment of the methyl ester with methyl-alcoholic ammonia for 2 days at −5° gave crystals of dimethyl *meso*tartramide, which were separated by decantation, washed with methyl alcohol, and crystallised from water; m. p. and mixed m. p. 257° (Found: OMe, 35·7. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·2%).

Identification of 2 : 3 : 5-*Trimethyl Glucosaccharo*-1 : 4-*lactone* 6-*Methyl Ester* (III).—Fraction (III) crystallised after several days. Trituration of the crystals with ether–light petroleum, followed by recrystallisation from ether, gave the ester (III) (0·4 g.), m. p. and mixed m. p. with a synthetic specimen, 78°; $[\alpha]_D^{18°}$ −10° in water (*c*, 0·7) (Found: C, 48·3; H, 6·5; OMe, 50·1; equiv., by heating with 0·02N-sodium hydroxide, 123. $C_{10}H_{16}O_7$ requires C, 48·4; H, 6·45; OMe, 50·0%; equiv. 124). After hydrolysis with barium hydroxide, the "residual OMe" (see above) was 37·0%, corresponding to ester OMe, 13% (Calc. for loss of 1OMe: residual OMe, 37·5%).

Direct treatment of fraction (III) with methyl-alcoholic ammonia gave a crystalline amide. This was triturated with ethyl alcohol–ether, collected, and recrystallised twice from ethyl alcohol and once from ethyl alcohol–ether. The *amide* (IV) of 2 : 3 : 5-trimethylsaccharic acid had m. p. 213° (decomp.); $[\alpha]_D^{17°}$ +18° in water (*c*, 2·0) (Found: C, 43·4; H, 7·4; N, 11·3; OMe, 37·4. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%). The same amide was obtained from the pure crystalline 2 : 3 : 5-trimethyl saccharolactone methyl ester. A Weerman test for α-hydroxy-amides carried out upon the diamide (20 mg.) was negative (for conditions, see Smith, J., 1939, 753).

Identification of 2 : 4 : 5-*Trimethyl Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (XI).—The syrup fraction (II) was allowed to react with methyl-alcoholic ammonia for 2 days at −5°. Removal of the solvent under reduced pressure gave a crystalline residue which was purified by several crystallisations from ethyl alcohol. The *amide* (XII) of 2 : 4 : 5-trimethyl saccharic acid had m. p. 194°; $[\alpha]_D^{18°}$ +21° in water (*c*, 1·0) (Found: C, 43·2; H, 7·5; N, 11·1; OMe, 38·1. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%).

This amide gave a depression of the m. p. when mixed with the amide (m. p. 193°) of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone prepared from 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester with methyl-alcoholic ammonia. The amide (XII) gave a negative Weerman test for α-hydroxy-amides (tested on 20 mg.). Fraction (IV) failed to give a crystalline amide, but fraction (V) afforded in small yield an unidentified crystalline amide, m. p. 203° (after recrystallisation from ethyl alcohol–ether). Fraction (VI) when treated with methyl-alcoholic ammonia yielded the monoamide of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone, m. p. and mixed m. p. 193° (after recrystallisation from ethyl alcohol).

Synthesis of 2 : 3 : 5-*Trimethyl Saccharo*-1 : 4-*lactone* 6-*Methyl Ester*.—A solution of methylglucofuranoside (18·7 g.) [prepared by the interaction of glucose with 1% methyl-alcoholic hydrogen chloride (Fischer, *Ber.*, 1914, **47**, 1982)] in pyridine (30 c.c.) which had been dried by three distillations over phosphoric oxide, was cooled in ice, and treated with trityl chloride (29 g.). The mixture was kept at room temperature for 3 days in a desiccator and shaken from time to time, and then warmed to 40° and poured with stirring into water. The syrupy product was triturated with water to remove as much pyridine as possible, and then dissolved in chloroform (200 c.c.). The chloroform solution was washed several times with dilute sulphuric acid to remove pyridine, with sodium hydrogen carbonate solution (twice), and water (once). After being dried (anhydrous magnesium sulphate), the solution was filtered and evaporated under reduced pressure to dryness. The 6-*trityl methylglucofuranoside* (VI) was a hard glass (Found: OMe, 6·3. $C_{26}H_{28}O_6$ requires OMe, 7·1%).

This compound (VI) was dissolved in acetone (150—200 c.c.) and treated slowly (2½—3 hours) with methyl sulphate (50 c.c.) and sodium hydroxide solution (200 c.c., 30%) at 35°, the mixture being stirred vigorously during the addition; the methylation was completed by heating to 60° to expel the acetone. The partly methylated product readily separated on the surface of the hot liquid; it was separated by decantation, washed once with hot water, and remethylated. After three methylations in this manner the methylated trityl compound was purified by dissolving it in chloroform (150 c.c.) and washing the solution with water. The chloroform solution was dried over anhydrous magnesium sulphate,

filtered, and evaporated to dryness under diminished pressure. The glassy product thus obtained was subjected to six methylations with silver oxide (20 g.) and methyl iodide (30 c.c.) at 45° for 8 hours. After each methylation the excess of the methyl iodide was distilled off, and the methylated trityl compound was isolated by means of acetone. The 6-*trityl* 2 : 3 : 5-*trimethyl methylglucofuranoside* (VII) thus obtained was a pale yellow glassy solid (Found: OMe, 24·8. $C_{29}H_{34}O_6$ requires OMe, 25·95%).

2 : 3 : 5-*Trimethyl methylglucofuranoside*. A solution of the 6-trityl 2 : 3 : 5-trimethyl methylglucofuranoside in ether (250 c.c.) was cooled in ice and saturated with hydrogen chloride. After standing for 30 minutes at 0°, the solution was removed from the ice-bath, kept at room temperature for 4 hours, and then extracted five times with water (50 c.c.). The combined aqueous extracts were neutralised with lead carbonate, filtered, and evaporated to dryness under diminished pressure. Extraction of the residue with acetone gave 2 : 3 : 5-*trimethyl methylglucofuranoside* as a colourless mobile liquid. This evidently contained some 2 : 3 : 5-trimethyl glucose because it reduced boiling Fehling's solution slightly. Hence, the liquid was dissolved in dry methyl alcohol (210 c.c.) containing hydrogen chloride (2 g.). After 18 hours, when the rotation of the solution had been constant for several hours, the solution was neutralised with silver carbonate, filtered, and evaporated to dryness. Extraction of the residue with ether gave 2 : 3 : 5-trimethyl methylglucofuranoside (9 g.), b. p. (bath temp.) 120°/0·01 mm., $n_D^{22°}$ 1·4540; $[\alpha]_D^{19°}$ −11° in water (*c*, 1·8) (Found: OMe, 52·0. $C_{10}H_{20}O_6$ requires OMe, 52·6%).

2 : 3 : 5-*Trimethyl glucose*. When a solution of 2 : 3 : 5-trimethyl methylglucofuranoside (1·9 g.) in 0·5N-sulphuric acid was heated on the boiling water-bath for 5 hours, the specific rotation changed from $[\alpha]_D$ −12° to + 14·5° (constant value). The solution was neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure. The syrupy residue was purified by extraction with ether and then distilled, giving 2 : 3 : 5-*trimethyl glucose* (VIII) as a colourless liquid (1·4 g.), b. p. (bath temp.) 140°/0·02 mm.; $n_D^{16°}$ 1·4690; $[\alpha]_D^{15°}$ +17° in water (*c*, 1·8) (Found: OMe, 41·0. $C_9H_{18}O_6$ requires OMe, 41·9%).

2 : 3 : 5-*Trimethyl γ-gluconolactone*. A solution of 2 : 3 : 5-trimethyl glucose (1·1 g.) in water (10 c.c.) was treated with bromine (0·7 c.c.) in the presence of lead carbonate (2 g.). After 2 days the excess of the bromine was removed from the solution by aeration. The solution was filtered, and hydrogen sulphide admitted until all the lead had been precipitated as sulphide, and thereafter treated with charcoal, filtered, and concentrated under diminished pressure to half volume. This solution, containing some hydrobromic acid produced by the action of hydrogen sulphide upon dissolved lead bromide, was then neutralised with silver oxide, and filtered before and after treatment with hydrogen sulphide. Evaporation of the solvent yielded a syrup which was extracted with ether. Two disillations of the product gave 2 : 3 : 5-*trimethyl γ-gluconolactone* as a colourless, fairly mobile liquid (0·7 g.), b. p. (bath temp.) 140°/0·05 mm.; $n_D^{17°}$ 1·4650; $[\alpha]_D^{18°}$ +62° initial value in water (*c*, 1·7); +59° (after 9 days); +54° (after 47 days) (mutarotation still incomplete) (Found: OMe, 43·0. $C_9H_{16}O_6$ requires OMe, 42·3%).

When this gluconolactone (0·1 g.) was heated with phenylhydrazine (0·06 g.) for 1 hour on the boiling water-bath, a crystalline phenylhydrazide was obtained in good yield. Trituration with ether to remove excess of phenylhydrazine, followed by recrystallisation from ethyl alcohol, gave the *phenylhydrazide* of 2 : 3 : 5-trimethyl gluconic acid, m. p. 156°; $[\alpha]_D^{16°}$ +32° in methyl alcohol (*c*, 0·4) (Found: C, 54·9; H, 7·35; N, 8·7; OMe, 28·1. $C_{15}H_{24}O_6N_2$ requires C, 54·9; H, 7·3; N, 8·5; OMe, 28·4%).

2 : 3 : 5-*Trimethyl glucosaccharo*-1 : 4-*lactone* 6-*methyl ester*. A solution of 2 : 3 : 5-trimethyl glucose (0·5 g.) was oxidised with nitric acid (3 c.c., *d* 1·42) by heating on the water-bath for ½ hour at 50° and for 2 hours at 95° (boiling water-bath). The mixture was diluted with water, and freed from nitric acid by distillation under reduced pressure. In the initial stages water was added from time to time to facilitate this operation and in the final stages methyl alcohol was added to eliminate any remaining nitric acid and water. The dry, acid residue was esterified by boiling for 8 hours with 1% methyl-alcoholic hydrogen chloride. Neutralisation of the mineral acid with silver carbonate, followed by removal of solvent under reduced pressure, yielded a syrupy product. This was purified by extraction with ether, followed by distillation, giving the methyl ester lactone as a colourless liquid (0·3 g.), b. p. (bath temp.) 135—140°/0·01 mm. The distillate crystallised spontaneously, and after recrystallisation from ethyl alcohol–ether–light petroleum, the 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone methyl ester (III) had m. p. 78°, alone or in admixture with a specimen prepared from glucosaccharo-1 : 4-lactone. This synthetic trimethyl ester lactone had $[\alpha]_D^{20°}$ −9·5° initial value in water (*c*, 0·9); −8° (after 3 days); + 6° (102 days) (Found: C, 48·6; H, 6·5; OMe, 49·5%). This compound may also be prepared by direct oxidation of 2 : 3 : 5-trimethyl methylglucofuranoside with nitric acid. There was no evidence of the presence of the characteristic 2 : 3 : 4-trimethyl glucosaccharolactone methyl ester in the material obtained by oxidation of the trimethyl glucose followed by esterification, showing that, throughout the series of experiments commencing with methyl-glucofuranoside, no ambiguity had arisen as a result of the latter being contaminated with methylglucopyranoside. Treatment of the synthetic 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone methyl ester (20 mg.) with methyl-alcoholic ammonia at room temperature for 2 days, followed by removal of the excess of the solvent gave the diamide of 2 : 3 : 5-trimethyl saccharic acid; $[\alpha]_D^{18°}$ +18° in water (*c*, 1·5); m. p. 213° (decomp.), undepressed on admixture with that prepared from saccharolactone (above).

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155. *Lactones of Mannosaccharic Acid. Part II. Synthesis of 2 : 3 : 5-Trimethyl Mannosaccharic Acid Diamide.*

By (MISS) D. HESLOP and F. SMITH.

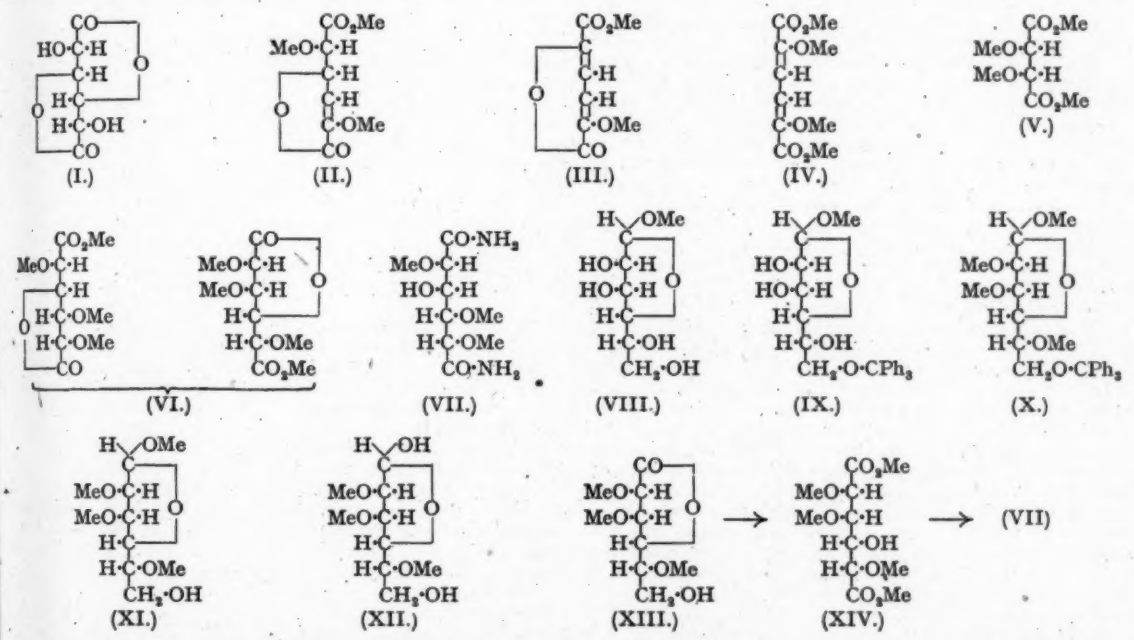
The trimethyl mannosaccharolactone methyl ester (VI), obtained previously by the action of diazomethane or the Purdie reagents upon mannosaccharodilactone (Haworth, Heslop, Salt, and Smith, this vol., p. 217), is shown by synthetic experiments to be the 2 : 3 : 5-*trimethyl* derivative. The synthesis involved the following series of reactions: α-methylmannofuranoside (VIII) ⟶ 6-*trityl α-methylmannofuranoside* (IX) ⟶ 6-*trityl* 2 : 3 : 5-*trimethyl α-methylmannofuranoside* (X) ⟶ 2 : 3 : 5-*trimethyl α-methylmannofuranoside* (XI) ⟶ 2 : 3 : 5-*trimethyl mannose* (XII) ⟶ 2 : 3 : 5-*trimethyl γ-mannonolactone* (XIII) ⟶ *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV) ⟶ 2 : 3 : 5-*trimethyl mannosaccharic acid diamide* (VII). The last was identical with the diamide from (VI).

METHYLATION of mannosaccharo-1 : 4 : 3 : 6-dilactone (I) either with silver oxide and methyl iodide or with diazomethane results in the formation of 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (II) as

the main product (Haworth, Heslop, Salt, and Smith, *loc. cit.*). Four other substances were isolated, *viz.*, a new trimethyl mannosaccharolactone methyl ester (from both methods of methylation) which is the subject of this communication, methyl dimethoxyerythrosuccinate (methyl dimethyl *meso*tartrate) (V) (from the methylation with silver oxide and methyl iodide), and two unsaturated substances (by both methods of methylation).

The first of the unsaturated compounds ($C_8H_8O_5$, m. p. 212°), having an absorption band with head at λ 3070 A. (ε, 12,000) moving to 3680 A. (ε, 14,000) upon addition of alkali, was identified as 6-carbomethoxy-3-methoxy-α-pyrone (III) (Haworth, Hirst, and Jones, J., 1938, 710; Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 449; Dippold, Schmidt, and Zeiser, *Ber.*, 1937, **70**, 2402); the second unsaturated substance ($C_{10}H_{14}O_6$, m. p. 140°), showing selective absorption with the head of the band at λ 3180 A. (ε, 24,000) in neutral and in alkaline solution, was not characterised, but it appeared to be a derivative of muconic acid. It may be considered to be derived from 2 : 5-dimethyl mannosaccharic acid by loss of the elements of two molecules of water from carbon atoms 2, 3, 4, and 5, and the formation of double bonds between C_2 and C_3 and between C_4 and C_5. One of the several possible geometric isomers is shown in (IV) and from the more recent work of Schmidt and Kraft (*Ber.*, 1941, **74**, 33) it is clear that the substance, m. p. 140°, has this structure.

The methyl dimethoxyerythrosuccinate probably arises as a result of oxidative cleavage of the six-carbon chain, and the trimethyl mannosaccharolactone methyl ester is formed from the dilactone by the opening of one lactone ring followed by methylation.



The disposition of the three ether methyl groups in the trimethyl mannosaccharolactone methyl ester (VI) was ascertained by the observation that the diamide (VII) derived from (VI) with methyl-alcoholic ammonia showed a negative Weerman test for α-hydroxy-amides (*Rec. Trav. chim.*, 1917, **36**, 16). Two of the methyl groups must therefore occupy positions 2 and 5. The third methyl residue may be attached either to C_3 or to C_4. Since the 2 : 3 : 5- and the 2 : 4 : 5-trimethyl derivative of mannosaccharic acid resulting from these two possibilities are identical, this lactone ester (VI), now under discussion, may be designated equally well either as 2 : 3 : 5- or as 2 : 4 : 5-trimethyl mannosaccharolactone methyl ester.

In view of the diverse nature of the reaction products obtained by the methylation of mannosaccharodilactone, it was deemed advisable to obtain further evidence in favour of the structure (VI) assigned to the trimethyl lactone methyl ester; in particular, it was important to prove that this ester (VI) was stereochemically related to mannose. The necessary evidence was forthcoming from the observation that a synthetic specimen of crystalline 2 : 3 : 5-*trimethyl mannosaccharic acid diamide* was found to be identical with the diamide (VII) prepared from the trimethyl lactone methyl ester (VI).

The synthesis of the diamide of 2 : 3 : 5-trimethyl mannosaccharic acid was performed as follows: Crystalline α-methylmannofuranoside (VIII), prepared by the method of Haworth, Hirst, and Webb (J., 1930, 651), gave 6-*trityl* α-*methylmannofuranoside* (IX) upon treatment with triphenylmethyl chloride. By means of silver oxide and methyl iodide, (IX) was converted into 6-*trityl* 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (X). When this compound was dissolved in ether containing hydrogen chloride, the trityl group was readily split off, and there was produced 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (XI). Hydrolysis of the latter was easily effected with dilute sulphuric acid, giving the corresponding 2 : 3 : 5-trimethyl mannose (XII) which, upon oxidation with bromine, yielded crystalline 2 : 3 : 5-*trimethyl* γ-*mannonolactone* (XIII), the presence of the

γ-lactone ring being indicated by the fact that an aqueous solution showed little or no mutarotation. Oxidation of the lactone (XIII) by heating with concentrated nitric acid yielded 2 : 3 : 5-trimethyl mannosaccharic acid, which was converted by methyl-alcoholic hydrogen chloride into *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV). When the latter was treated with methyl-alcoholic ammonia it afforded the corresponding diamide of 2 : 3 : 5-trimethyl mannosaccharic acid, identical with (VII).

The characterisation of the 2 : 3 : 5-trimethyl mannosaccharolactone methyl ester as a methylation product of mannosaccharodilactone indicates that at least one of the lactone rings in the dilactone (I) is of the γ-type (see Schmidt and Kraft, *loc. cit.*).

Experimental.

Synthesis of 2 : 3 : 5-*Trimethyl Mannosaccharic Acid Diamide.*—6-*Trityl* α-*methyl*-d-*mannofuranoside* (IX). To a solution of crystalline α-methylmannofuranoside (1·89 g.) (prepared by the method of Haworth, Hirst, and Webb, J., 1930, 651) in dry pyridine (10 c.c.), there was added triphenylmethyl chloride (2·9 g.); the mixture was warmed to 60° and then kept for 7 days at room temperature. Water (150 c.c.) was now added, and the product extracted with chloroform (150 c.c.). The chloroform solution was washed with N-sulphuric acid (five times), aqueous sodium bicarbonate (twice), and water (once). The chloroform solution was dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness under diminished pressure. The colourless glassy product, 6-*trityl* α-*methylmannofuranoside*, $[\alpha]_D^{17°}$ +40° in chloroform (*c*, 1·8), showed no tendency to crystallise (yield, 4·3 g.) (Found: OMe, 6·0. $C_{26}H_{28}O_6$ requires OMe, 7·1%).

6-*Trityl* 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (X). The above trityl compound was methylated with silver oxide and methyl iodide in the usual manner to afford the *furanoside* (X) [Found: OMe, 21·6 (after 6 methylations); 22·3 (after 8); 22·4 (after 10). $C_{29}H_{34}O_6$ requires OMe, 25·9%] as a colourless viscous syrup having $[\alpha]_D^{16°}$ +19° in chloroform (*c*, 1·8) (yield, 4·0 g.).

2 : 3 : 5-*Trimethyl* α-*methylmannofuranoside* (XI). A solution of the 2 : 3 : 5-trimethyl compound (X) (4·0 g.) in ether (130 c.c.) was cooled in an ice-bath and saturated with hydrogen chloride. The mixture was kept for 1 hour at 0°, then allowed to acquire room temperature (1 hour), and evaporated thereat under diminished pressure to half its volume to remove as much hydrogen chloride as possible. The ethereal solution was then extracted six times with water (20 c.c.). The aqueous extracts were combined, neutralised with lead carbonate, filtered, and evaporated to dryness under reduced pressure. Extraction of the dry residue with ethyl alcohol afforded a syrup which was extracted with ether. Removal of the solvent gave a syrup (1·25 g.) which was treated with 1% methyl-alcoholic hydrogen chloride (50 c.c.) at room temperature for 17 hours in order to convert any 2 : 3 : 5-trimethyl mannose into the corresponding glycoside. Neutralisation of the mineral acid with silver carbonate, followed by filtration and removal of solvent, yielded a syrup which upon distillation gave 2 : 3 : 5-*trimethyl methylmannofuranoside* as a colourless, mobile liquid (0·8 g.), b. p. (bath temp.) 115—120°/0·03 mm., $n_D^{16°}$ 1·4580, $[\alpha]_D^{18°}$ +54° in water (*c*, 1·3) (Found: OMe, 51·9. $C_{10}H_{20}O_6$ requires OMe, 52·6%). A small fraction (0·2 g.) was obtained, b. p. (bath temp.) 120—140°/0·03 mm., $n_D^{19°}$ 1·4638, but this was not pure and so was rejected.

2 : 3 : 5-*Trimethyl* γ-d-*mannonolactone* (XIII). A solution of the foregoing compound (XI) (0·74 g., first fraction) in 0·1N-sulphuric acid (40 c.c.) was heated on the boiling water-bath; the specific rotation changed in 80 minutes from +52° (initial value) to +28° (equilibrium value). After a further hour's heating the solution was neutralised with barium carbonate, heated with a little charcoal until the barium sulphate had settled, and then filtered, the residue being well washed with boiling water. The filtrate was evaporated to dryness under reduced pressure, giving syrupy 2 : 3 : 5-trimethyl mannose (0·63 g.), which reduced Fehling's solution.

This syrup (0·62 g.) was dissolved in water (20 c.c.) and oxidised with bromine (1 c.c.) at room temperature for 3 days. The excess of bromine was removed by aeration, the solution neutralised with silver oxide, treated with a little charcoal, filtered before and after treatment with hydrogen sulphide, and then evaporated under reduced pressure to dryness. The syrupy product was purified by extraction with acetone–ether and then lactonised by heating in a vacuum for 3 hours at 70—80°. On keeping, the lactone (0·3 g.) crystallised spontaneously. After purification by distillation, followed by recrystallisation from ethyl alcohol–light petroleum, the 2 : 3 : 5-*trimethyl* γ-*mannonolactone* had m. p. 118°, $[\alpha]_D^{18°}$ +67° (initial value) in water (*c*, 1·0) changing in 22 days to +63·5° (mutarotation still incomplete). The sodium salt, prepared by heating the lactone with a slight excess of sodium hydroxide solution, showed $[\alpha]_D^{18°}$ −27°, and upon acidification the solution had $[\alpha]_D^{18°}$ −31°. The lactone is soluble in water, ethyl and methyl alcohol, acetone, and ethyl acetate, sparingly soluble in ether, and insoluble in light petroleum (Found: C, 49·0; H, 7·5; OMe, 41·6. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%).

Treatment of the pure crystalline lactone (20 mg.) with methyl-alcoholic ammonia (2 c.c.) for 2 days at − 5° gave the *amide* of 2 : 3 : 5-trimethyl mannonic acid, which crystallised upon removal of the solvent; m. p. 162°, $[\alpha]_D^{18°}$ − 28° in water (*c*, 1·0) (after recrystallisation from ethyl alcohol or ethyl alcohol–acetone) (Found: OMe, 38·2. $C_9H_{19}O_6N$ requires OMe, 39·3%).

2 : 3 : 5-*Trimethyl mannosaccharic acid diamide* (VII). A solution of the lactone (0·3 g.) in nitric acid (5 c.c.; *d* 1·42) was heated on the water-bath for 1 hour at 50° and for 5 hours at 85—95°. The solution was diluted with water and freed from nitric acid by distillation under diminished pressure, water and then methyl alcohol in the final stages being added to complete the removal. The syrupy acid residue was dried by heating in a vacuum and then esterified by boiling with 1% methyl-alcoholic hydrogen chloride (50 c.c.) for 8 hours. The solution was neutralised with silver carbonate, filtered, and evaporated to dryness under diminished pressure. Distillation of the syrupy residue gave *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV) (0·2 g.), b. p. (bath temp.) 160°/0·07 mm., $n_D^{17°}$ 1·4465, $[\alpha]_D^{18°}$ −21° in methyl alcohol (*c*, 0·8) (Found: OMe, 54·1. $C_{11}H_{20}O_8$ requires OMe, 55·4%).

This ester (XIV) (0·1 g.) was treated with methyl-alcoholic ammonia for 4 days at −5°. By this time most of the *diamide* of 2 : 3 : 5-trimethyl mannosaccharic acid had crystallised. The crystals were washed by decantation with methyl alcohol and then purified by recrystallisation from water; m. p. 258° (decomp.), $[\alpha]_D^{18°}$ −39° in water (*c*, 0·6). This diamide gave no depression of m. p. when mixed with the diamide of 2 : 3 : 5-trimethyl mannosaccharic acid obtained from mannosaccharodilactone. A Weerman test upon this synthetic amide (20 mg.) was negative (Found: C, 43·3; H, 7·35; N, 11·25; OMe, 37·7. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%).

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156. *Lactones of Mannosaccharic Acid. Part III. Isomerisation of Mannosaccharodilactone with Alkali.*

By (Miss) D. Heslop and F. Smith.

The unexpected and hitherto unexplained reducing properties of mannosaccharodilactone (I) in alkaline solution, or in acid solution after pre-treatment with alkaline reagents, are shown to be due to the conversion of the dilactone by alkaline reagents into the *enol* of 5-*keto*-4-*deoxymannosaccharo*-3 : 6-*lactone* (II). This was isolated in the crystalline condition and its structure elucidated; it shows to a marked degree all the reducing properties of mannosaccharodilactone.

Ozonolysis of (II) gave oxalic acid and erythruronic acid (III), the latter being oxidised with bromine to dihydroxyerythrosuccinic acid (*meso*tartaric acid) (IV). Methylation of the enol (II) with diazomethane afforded the 5-*methyl ether* of the *enol* of 5-*keto*-4-*deoxymannosaccharo*-3 : 6-*lactone* 1-*methyl ester* (V), which was converted by the agency of silver oxide and methyl iodide into crystalline 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (VI). The structure of the latter was proved by ozonisation, a process which led to the formation of oxalic acid and 3-methyl *d*-erythruronic acid (VII). Oxidation of (VII) with bromine yielded the known 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid (VIII), characterised as the crystalline bismethylamide (X). A closer examination of the reaction of chlorine with the reducing enol (II) has been made. This reaction is partly one of addition of chlorine to the double bond between C_4 and C_5, as shown by the formation of a crystalline *dichloro-compound* (XVII).

Methylation of mannosaccharo-1 : 4-3 : 6-dilactone (I) either with silver oxide and methyl iodide or with diazomethane has been shown to give 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (VI) (Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 449; Haworth, Heslop, Salt, and Smith, this vol., p. 217). This analogue

Fig. 1.

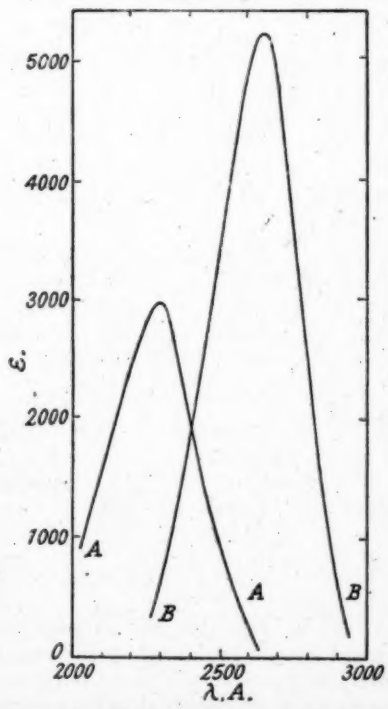


Fig. 2.

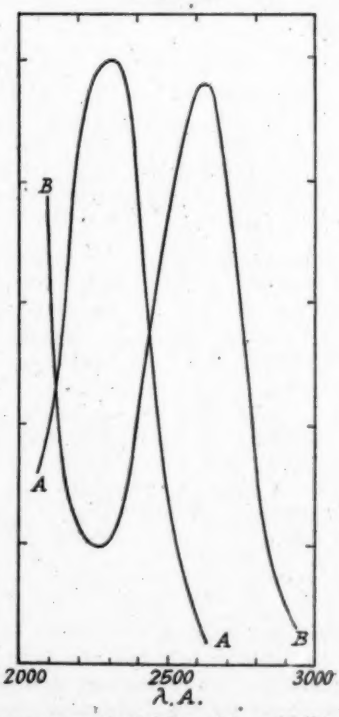


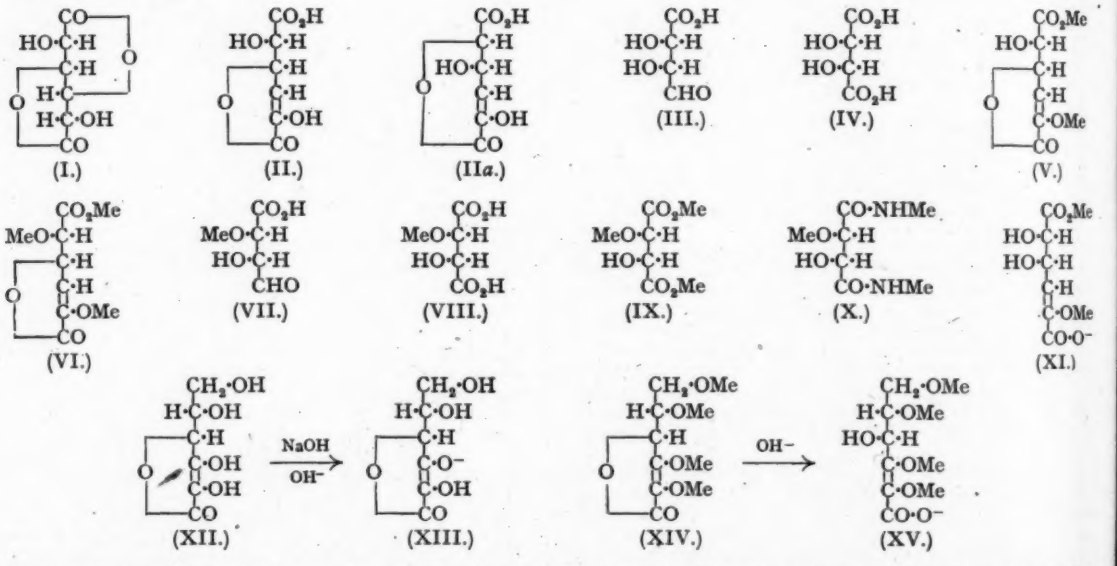
Fig. 1.—A. *Mannosaccharodilactone after treatment with aqueous alkali followed by acid* (10 *mg.* %).
B. *Mannosaccharodilactone in aqueous alkaline solution* (3 *mg.* %).

Fig. 2.—A. *Monohydrate of enol of* 5-*keto*-4-*deoxymannosaccharo*-3 : 6-*lactone* (*II*) *in water* (5 *mg.* %).
B. " " " " " " (*II*) *in aqueous alkali* (5 *mg.* %).

of ascorbic acid was found to display an absorption band at λ 2290 A. (Fig. 4); it reacted with chlorine or bromine, and decolorised alkaline potassium permanganate in the cold. In addition it reacted with iodine in alkaline solution, a process accompanied by the formation of small amounts of iodoform. When mannosaccharodilactone itself is treated with alkaline reagents a substance is produced in solution which resembles in its properties 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (VI). For instance, a solution of the dilactone which has been made alkaline and then acidified shows a band at λ 2290 A. in acid solution moving to λ 2630 A. in alkaline solution (Fig. 1); it reacts with chlorine, bromine, and potassium permanganate. The crystalline dilactone reduces Fehling's solution actively and it reacts with iodine in alkaline solution, giving small amounts of iodoform. These facts led to the suggestion that the reactive substance,

obtained in solution from mannosaccharodilactone by the agency of alkaline reagents, was structurally related to (VI). Such differences as there were between the reactive substance and (VI), *e.g.*, the failure of the latter to reduce Fehling's solution, seemed to be due to the fact that the former was the unmethylated form of (VI).

The proof that this deduction was correct is based upon the following experimental facts. Treatment of mannosaccharodilactone with sodium methoxide in alcohol gave a sodium derivative which reduced Fehling's solution, reacted with alkaline iodine, and showed strong selective absorption with the head of the band at λ 2630 A. An acidified aqueous solution of the sodium derivative showed a band at λ 2290 A., and reacted readily with chlorine, bromine, and potassium permanganate. Addition of methyl-alcoholic hydrogen chloride to the sodium derivative, followed by removal of sodium chloride and solvent, afforded a syrupy product which displayed all the properties of a solution prepared by treatment of the dilactone with alkali followed by acid. If the reactive substance, obtained from the sodium derivative referred to above, is the unmethylated form of 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (VI), then it is clear that the oxidative methods applied to the determination of the structure of the latter should be applicable to the former. This proved to be the case, for when the syrupy reactive substance was subjected to ozonolysis there were formed oxalic acid and an aldehydic acid, erythruronic acid (III). The formation of the extra carboxyl group together with an aldehydic group as a result of ozonisation confirmed the presence of the system ·CH:C(OH)· in the reactive substance. Moreover, the isolation of oxalic acid and the erythruronic acid (III) and the absence of glyoxylic acid proved that the double bond in this system must engage C_4 and C_5, and that the hydroxyl group in it is attached to C_5 and not to C_4, while the hydrogen in the unsaturated system must be linked to C_4, thus ·C_4(H):C_5(OH)·. If this were not the case and the system was reversed, as in ·C_4(OH):C_5(H)·, it is clear that ozonisation would give rise to glyoxylic acid and *meso*tartaric acid. The structure of the strongly reducing erythruronic acid (III) was ascertained by its oxidation with bromine to dihydroxyerythrosuccinic acid (*meso*tartaric acid) (IV), recognised in the form of its characteristic crystalline methyl ester and its corresponding diamide.



These experimental facts were in accordance with the formula (II), the unmethylated form of (VI), for the reactive substance, but it is clear that the facts could also be explained by the structure (II*a*) which contains the pyrone ring and not the furone ring as in (II).

It became possible, however, to distinguish between these two possibilities when the reactive substance became available in the pure crystalline form. This was achieved by treatment of mannosaccharodilactone in dry methyl alcohol with sodium methoxide, in order to form the sodium derivative of the reactive substance, followed by liberation of the free organic acid by methyl-alcoholic hydrogen chloride. This procedure afforded the crystalline reactive *enol* of *5-keto-4-deoxymannosaccharo-3 : 6-lactone* (an isomeric form of the dilactone) (m. p. 142°, $[\alpha]_D$ − 48°) which readily formed a *monohydrate* (m. p. 82°). This acid substance showed an absorption band at λ 2290 A. (Figs. 2 and 3), moving to λ 2630 A. on addition of sodium hydroxide. In aqueous solution this reactive acid shows slow mutarotation, a change attended by a gradual decrease in the intensity of the band at λ 2290 A.; this observation suggested that a lactone ring was present in the reactive substance and that this ring, containing the unsaturated system, is essential for selective absorption of light. This behaviour is analogous to that of 2 : 3 : 4 : 6-tetramethyl *l*-ascorbic acid (XIV) (Haworth, Hirst, and Smith, J., 1934, 1556) and 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone (Smith, this vol., p. 515), for both these substances show selective absorption in the ultra-violet region of the spectrum, the former at λ 2350 A. and the latter at λ 2290 A., and in alkaline solution, when the rings are opened, no selective absorp-

tion of light is displayed by either substance. The reactive substance (m. p. 142°) (II) reduced Fehling's solution actively, it reacted with chlorine and bromine, and with iodine in alkaline solution to give small amounts of iodoform. A closer examination showed that, whereas the original mannosaccharodilactone reacted with four atomic proportions of iodine in alkaline solution, yet (II) reacted with six atomic proportions under the same conditions, these six probably being consumed in the oxidation of the system $CHR{:}C(OH)R_2$ to $R{\cdot}CO_2H + R_2{\cdot}CO_2H$. This difference in the amount of iodine consumed by the two substances may be due to the fact that alkaline reagents effect only a partial conversion (two-thirds) of the dilactone into the substance (II). It is suggested that a mixture of the sodium derivative of the reactive substance and normal sodium mannosaccharate is formed. Support for this view is found in the fact that, after treatment of mannosaccharodilactone with sodium hydroxide, followed by an equivalent amount of acid, there can be isolated unchanged mannosaccharodilactone. This partial conversion of the dilactone into the isomeric reactive substance is also believed to be responsible for the observation that, although a solution of manno-

FIG. 3. FIG. 4.

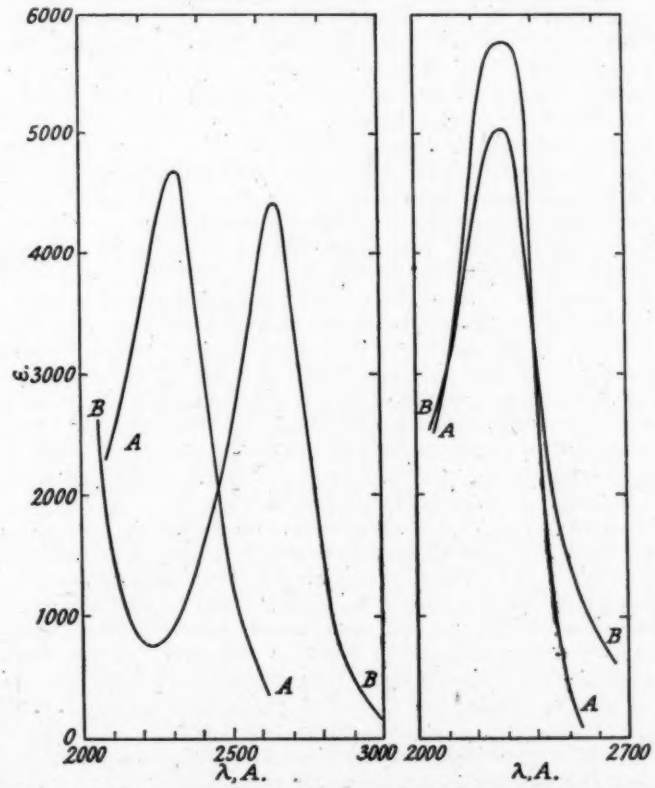


FIG. 3.—A. *The enol of 5-keto-4-deoxymannosaccharo-3 : 6-lactone (II) in aqueous solution* (5 mg. %).
B. ,, ,, ,, ,, ,, *(II) in aqueous sodium hydroxide* (5 mg. %).
FIG. 4.—A. *2 : 5-Dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (VI) in water* (5 mg. %).
B. *5-Methyl Δ^4-* ,, ,, ,, ,, *(V) in water* (5 mg. %).

saccharodilactone treated successively with sodium hydroxide and sulphuric acid reacted with two atomic proportions of chlorine, yet the pure crystalline reactive substance (II) accounted for four atomic proportions.

Ozonisation of the crystalline reactive substance (II) (m. p. 142°) gave oxalic acid and the aldehydic acid, erythruronic acid (III), identified by its conversion into dihydroxyerythrosuccinic acid (*meso*tartaric acid) (IV). By these results it became abundantly clear that (II) was identical with the reactive substance present in the syrupy product first examined, and that the reactions already described for the latter were due to the presence of (II) in it. Inspection of the formulæ (II) and (II*a*) revealed that the reactive compound could be represented by either of these, for both explained the experimental results.

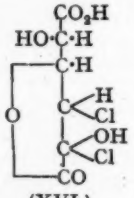
The proof that the reactive crystalline substance has the structure (II) and not (II*a*) was based on the following observations. When (II) was allowed to react with ethereal diazomethane, the introduction of two methoxyl groups was smoothly effected with the formation of a neutral substance (V), the *5-methyl ether* of the enol of 5-keto-4-deoxymannosaccharo-3 : 6-lactone 1-methyl ester. The latter, like the original substance (II), still exhibited the band at λ 2290 A. (Fig. 4), but unlike (II), which showed a band at λ 2630 A. in alkaline solution, (V) exhibited no selective absorption in alkaline solution; alkaline reagents would therefore appear to open the ring of (V) while they do not affect the ring in the original unmethylated substance (II).

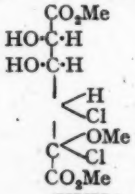
When the enolic hydroxyl at C_5 is free, as in (II), the reactive hydrogen in it shows a tendency to be liberated as a proton, a process leading to the stabilisation of the ring system; thus, in alkaline solution a sodium derivative is formed by loss of a proton at C_5, the unsaturated furone ring responsible for the absorption band remains intact, and hence a band at λ 2630 A. is displayed. In the case of the dimethyl derivative (V) the alkaline reagents cannot affect the enolic hydroxyl at C_5, for this is now blocked, and consequently the furone ring system is unable to stabilise itself by losing a proton from C_5 and opens under the influence of excess of hydroxyl ions, with the formation of a normal open-chain sodium salt which shows no selective absorption band. This rather curious behaviour of the reactive substance is paralleled by that of ascorbic acid (XII), the furone ring of which is also stable to alkali; thus the absorption band of ascorbic acid shown at λ 2450 A. in aqueous solution moves to λ 2650 A. on addition of sodium hydroxide, owing to liberation of a proton from the enolic hydroxyl at C_3 as in (XIII) and the formation of sodium ascorbate in which the unsaturated furone ring system is still present. On the other hand, 2 : 3 : 5 : 6-tetramethyl ascorbic acid (XIV), resembling closely the dimethyl derivative (V), shows a band at λ 2350 A. when the furone ring is intact, whereas upon the addition of sodium hydroxide the ring opens and the selective absorption band disappears.

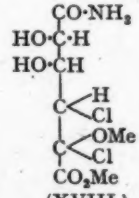
The neutral dimethyl derivative (V) no longer reduced Fehling's solution, showing that the grouping ·CH:C(OH)· (responsible for reducing activity) was no longer present as such but was now in the methylated form ·CH:C(OMe)·. The reactivity of the dimethyl derivative (V) towards chlorine and bromine, associated with the presence of a double bond was, however, still exhibited. Further methylation of (V) with silver oxide and methyl iodide yielded the crystalline trimethyl derivative (VI). The latter showed selective absorption in the ultra-violet region of the spectrum, the head of the band being at λ 2290 A. (Fig. 4); in alkaline solution the furone ring of (VI) opens and the absorption band disappears. The physical properties of this trimethyl derivative (VI) were shown to be identical with those of 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester, previously prepared by simultaneous methylation and isomerisation of mannosaccharo-1 : 4-3 : 6-dilactone (Haworth, Heslop, Salt, and Smith, *loc. cit.*), and the identity of the two was established by ozonolysis, a process which afforded oxalic acid and the 3-monomethyl erythruronic acid (VII). Oxidation of the latter with bromine gave the corresponding dibasic acid, 3-hydroxy-2-methoxy-*l*-erythrosuccinic acid (VIII), which, by means of methyl-alcoholic hydrogen chloride, was smoothly transformed into its methyl ester (IX). This was identified by its conversion into the known crystalline bismethylamide (X) (Haworth, Heslop, Salt, and Smith, *loc. cit.*; Heslop, Salt, and Smith, this vol., p. 225). The presence of the 3 : 6-lactone ring in the trimethyl derivative (VI) and therefore in (II) was thus established. The crystalline unsaturated acid substance (m. p. 142°) obtained by successive treatments of the dilactone with alkali and acid is consequently represented by the furone structure (II) and not by the pyrone structure (II*a*), being therefore the mono-enol of 5-*keto*-4-*deoxymannosaccharo*-3 : 6-*lactone*. This is the substance which is responsible for the unique reducing properties displayed by mannosaccharodilactone.

As would be expected from the close structural relationship between (II) and ascorbic acid (XII), the properties of the two compounds are very similar: both show selective absorption of light, the former having a band at λ 2290 A. and the latter at λ 2450 A., and both behave in the same curious way when treated with sodium hydroxide, (II) losing a proton from the hydroxyl group at C_5, and (XII) one from the hydroxyl group at C_4 to give the ascorbate ion (XIII). In both cases the unsaturated ring system appears to remain unaffected, for in alkaline solution (II) has a band at λ 2630 A. and (XII) one at λ 2650 A. The activity of the enolic hydroxyl groups in these two compounds is also demonstrated by treatment with ethereal diazomethane: (II) gives a 5- and (XII) a 4-methyl ether (the C atom of the ·CH_2·OH group is referred to as C_1) (Haworth, Hirst, and Smith, *loc. cit.*).

Both (II) and (XII) show strong reducing activity towards Fehling's solution, but the latter reduces silver nitrate in the cold whereas (II) is without action upon this reagent.


(XVI.)


(XVII.)


(XVIII.)

The enol (II) and ascorbic acid react immediately with potassium permanganate in acid solution, with chlorine, and with bromine. In their behaviour towards iodine, however, they differ markedly inasmuch as (XII) reacts quickly with two atomic proportions and (II) reacts with only a small quantity of iodine.

A closer examination of the reaction of the enol (II) and ascorbic acid with chlorine has also established a great difference between the two. Ascorbic acid reacts with chlorine in the same way as it does with iodine, *viz.*, as a reducing agent; two hydroxyl groups appear to be added to the double bond, and two chloride ions are liberated in the process. Moreover, the reaction is reversible, for treatment of the fresh chlorine-oxidised solution with hydrogen sulphide regenerates the ascorbic acid (Herbert, Hirst, Percival, Reynolds, and Smith, J., 1933, 1270). The enol (II), however, consumed four, and not two, atomic proportions of chlorine in the process, which could not be reversed with hydrogen sulphide. Chlorine oxidation of both (II) and (XII)

affords substances which show no selective absorption of light; the latter gives dehydroascorbic acid (2 : 3-diketogulonolactone), probably as a hydrate, as the sole product, whereas the only definite substance isolated from the former was a dichloro-compound (XVI) which probably arises as a result of the addition of chlorine to the double bond of (II). The other chlorine oxidation products were not identified.

The dichloro-compound has been characterised by isolation of the crystalline methylated *dichloro-ester* (XVII), the saturated character of which is shown by the absence of activity towards chlorine and bromine and also by the fact that its aqueous solutions exhibited no selective absorption of light. The crystalline neutral dichloro-compound (XVII) was found to contain three methoxyl groups, two of which were esteric in character since they could be eliminated by warming with barium hydroxide solution. This was confirmed by the isolation of the corresponding dibasic *acid* which contained one ether methoxyl group. The conversion of the dichloro-ester (XVII) into the crystalline monoamide (XVIII), possessing two methoxyl groups, and the fact that this amide showed a positive Weerman test for α-hydroxy-amides, indicated that the ether methoxyl group in the amide (XVIII), and therefore in the ester (XVII), must have been attached either to C_3 or to C_5. The location of this methoxyl group is not certain but it seems improbable that the short time of the reaction of (XVI) with diazomethane would effect the introduction of a methyl group into the secondary alcoholic group at C_3. Since the reaction of the enol (II) with chlorine involves to some extent addition of halogen to the double bond, it is clear why only a portion of the chlorine used is detectable as chloride ion and it also explains why the reaction with iodine proceeds only to a small extent.

Experimental.

Properties of Mannosaccharodilactone.—Aqueous solutions of the dilactone (for preparation, see Haworth, Heslop, Salt, and Smith, this vol., p. 217) show a faint acid reaction to litmus paper; they show no selective absorption (tested at 200 mg. %) but upon addition of sodium hydroxide solution isomerisation takes place with the formation of the enol of 5-keto-4-deoxymannosaccharolactone (II). The presence of the latter is shown by the alkaline solution exhibiting a band at λ 2630 A. which moves to λ 2290 A. upon acidification of the solution (Fig. 1) (Haworth, Heslop, Salt, and Smith, *loc. cit.*). Alkaline solutions of the dilactone reduce Fehling's solution actively and quickly decolorise potassium permanganate. The acidified solutions showing the band at λ 2290 A. react immediately with chlorine water and bromine water, and also decolorise potassium permanganate.

Action of Iodine in Alkaline Solution upon Mannosaccharodilactone.—To a solution of the dilactone (0·1013 g.) in water (20 c.c.), 0·1N-sodium hydroxide (87 c.c.) and 0·1N-iodine (50 c.c.) were added. After 90 minutes the solution was acidified with N-sulphuric acid (10 c.c.), and the excess of the iodine back-titrated with 0·1N-sodium thiosulphate (28·0 c.c.) (a blank experiment was carried out at the same time under the same conditions). In two similar experiments, using 0·1005 g. and 0·1028 g. of dilactone, 21·4 c.c. and 22·3 c.c. of 0·1N-iodine, respectively, were consumed. These results indicate that 1 g.-mol. of the dilactone reacts in alkaline solution with approximately 4 g.-atoms of iodine. Small amounts of iodoform are produced in these oxidations, and the presence of oxalic acid may also be demonstrated (see Haworth, Heslop, Salt, and Smith, *loc. cit.*).

Treatment of Mannosaccharodilactone with Sodium Hydroxide.—A solution of the dilactone (1 g.) in water (18 c.c.), treated with N-sodium hydroxide (23 c.c.), showed the following change in specific rotation: − 55° (initial value); − 41° (after 0·5 hr.); − 18° (1·5 hrs.); − 12·5° (2 hrs.); − 10·5° (3·5 hrs.); − 11·5° (15·5 hrs.); − 13° (20 hrs.); − 13·5° (27 hrs.); − 14° (72 hrs.); − 14·5° (87 hrs.). To this alkaline solution N-sulphuric acid (22·5 c.c.) was added, and the solution, which showed $[\alpha]_D$ +5°, was evaporated to dryness under reduced pressure. Extraction of the residue with methyl alcohol afforded a brownish-yellow syrup which was purified by extraction with ethyl alcohol. On keeping, the syrup crystallised, and after removal of adhering syrup from the crystals by trituration with ethyl alcohol followed by crystallisation from ethyl alcohol, mannosaccharodilactone (0·1 g.) was obtained, m. p. and mixed m. p. 180° (decomp.), $[\alpha]_D^{18°}$ +195° (initial value in water; *c*, 1·3).

Reaction of Mannosaccharodilactone treated successively with Alkali and with Acid.—(*a*) *With potassium permanganate.* A solution of the dilactone (0·108 g.) in water (10 c.c.) was treated with N-sodium hydroxide (3 c.c.) for 3 minutes, followed by N-sulphuric acid (5 c.c.). This acidified solution was titrated with 0·1N-potassium permanganate (8·7 c.c.) until a permanent pink colour persisted. The oxidised solution showed $[\alpha]_{5780}^{18°}$ +83·5° (initial value). In a second experiment the dilactone (0·051 g.), after pretreatment with N-sodium hydroxide followed by acid, required 3·85 c.c. of 0·1N-permanganate.

(*b*) *With chlorine water.* A solution of the dilactone (0·1 g.) in water (5 c.c.) was treated with 0·1N-sodium hydroxide (13 c.c.) for 1 minute and then acidified with 0·1N-sulphuric acid (13·5 c.c.). The solution was titrated with 0·083N-chlorine water (14·1 c.c.), starch–iodide paper being used as indicator (Calc. for two atomic proportions of chlorine: 13·85 c.c.). This chlorine-treated solution, which showed no selective absorption band, had $[\alpha]_{5780}^{12°}$ +84° (initial value); no band appeared upon treatment of the solution with hydrogen sulphide.

A solution of the dilactone (0·077 g.) in water (6·5 c.c.) having $[\alpha]_{5780}^{18°}$ +209°, treated with N-sodium hydroxide (1·5 c.c.), had $[\alpha]_{5780}^{18°}$ −57°. After the addition of N-sulphuric acid (1·5 c.c.), the solution, now containing the enol (II), had $[\alpha]_{5780}^{18°}$ −27°. Chlorine water was added every 5 minutes until a slight excess was present, and the change in specific rotation observed:

Chlorine water added, c.c. ...	1	2	3	3·5	4	4·5	5	5·5	6	6·5	7	7·5	8
$[\alpha]_D$	−19°	−12°	−8°	−3·5°	±0°	+5·5°	+9·5°	+12°	+16°	+21°	+25°	+31°	+36·5°
Chlorine water added, c.c. ...	8·5	9·0	9·5	10	10·5	11	11·5	12	12·5	13	13·5	14	
$[\alpha]_D$	+42°	+46°	+49·5°	+53·5°	+57·5°	+61·5°	+65·5°	+70°	+74·5°	+76°	+78°	+79·5°	

The chloride ion present in this oxidised solution was precipitated as silver salt by means of silver nitrate solution in the presence of nitric acid, and 75% of the chlorine used was thus recovered.

Treatment of Mannosaccharodilactone with Sodium Methoxide.—The dilactone (5 g.) was dissolved in hot methyl alcohol (400 c.c.) and while still warm the solution was treated with 3 equivs. of sodium methoxide in methyl alcohol (73 c.c.; 1·18N); a pale yellow solid separated. After 3 minutes, a small portion of the solution was centrifuged and the sodium derivative was washed on the centrifuge with methyl alcohol, then with ether, and finally dried in a vacuum (Found: Na, 16·6%). In aqueous acidified solution this sodium derivative showed a selective absorption band at λ 2290 A. (ε, 2000 approx.) moving upon addition of sodium hydroxide to λ 2630 A. (ε, 2500 approx.). An aqueous solution of the sodium derivative had $[\alpha]_D$ + 1° (initial value) (*c*, 2·2); + 4·5° (after 9 hrs.); + 10° (1 day); + 15°

(3 days); + 20° (4 days) (constant for 1 day). The freshly prepared sodium derivative had iodine number, 186. An aqueous solution of the sodium derivative which had undergone complete mutarotation had iodine number, 208.

The main bulk of the solution containing the sodium derivative was treated with methyl alcohol (45 c.c.) containing hydrogen chloride equivalent to the sodium methoxide used in the isomerisation. Removal of the sodium chloride by filtration, and of the solvent by distillation under diminished pressure, gave a colourless syrup. This syrup, which reacted acid to Congo-red, showed in aqueous solution a band at λ 2290 A. (ε, 3500 approx.; *c*, 5 mg. %), moving to λ 2630 A. (ε, 4000 approx.; *c*, 5 mg. %) upon addition of sodium hydroxide. It readily reacted with chlorine and bromine, and decolorised acid potassium permanganate immediately. The syrupy product reduced Fehling's solution actively on warming.

Ozonisation. A solution of the syrup, obtained in the previous experiment, in glacial acetic acid (50 c.c.) was subjected to the action of a stream of ozonised oxygen at room temperature: $[\alpha]_D$ − 17° (initial value); − 14° (after 1 hr.); − 12·5° (2 hrs.); ± 0° (5 hrs.); + 4° (6 hrs.); + 5° (7 hrs.); + 7·5° (7½ hrs.); + 9° (8 hrs.); + 10·5° (9 hrs.). After 6 hrs. the solution ($[\alpha]_D$ + 4°) contained oxalic acid (tested with calcium chloride) and reduced Fehling's solution in the cold. The solution was diluted with water, and freed from acetic acid by distillation under diminished pressure, small amounts of water being added at intervals. The syrupy product thus obtained was acidic; oxalic acid was readily shown to be present in it (calcium chloride test; and formation of phenylhydrazine oxalate, m. p. 178°). The syrupy product reduced Fehling's solution in the cold. No glyoxylic acid could be detected.

Oxidation of Ozonolysis Product with Bromine.—Isolation of dihydroxyerythrosuccinic acid (IV). While still containing oxalic acid and probably some mannosaccharolactone (since the whole of the dilactone is not transformed into the enol), the syrupy product was dissolved in water (20 c.c.) and treated with bromine (1 c.c.) at room temperature. After 12 hours a portion of the solution, when freed from bromine by aeration, still reduced Fehling's solution in the cold. This could not have been due to mannosaccharodilactone, since this does not reduce Fehling's solution in the cold, or to any of the monoenol of 5-keto-4-deoxymannosaccharolactone which had escaped ozonisation, because the solution showed no selective absorption band (tested at 50 mg. %). Hence more bromine (1 c.c.) and barium carbonate (4 g.) were added. After 10 hours, oxidation was complete and the solution was freed from the excess of the bromine by aeration. The solution was neutralised as far as possible by grinding it with the barium carbonate and then finally by careful addition of barium hydroxide (0·3N) until it gave a faint pink colour with phenolphthalein. The white precipitate was filtered off, washed with water, and then triturated with dilute acetic acid to remove barium carbonate. The barium salts of oxalic and dihydroxyerythrosuccinic (*meso*tartaric) acids were filtered off, washed with water, alcohol, and dried in a vacuum at 80°.

All filtrates, obtained in the operations after the addition of the 0·3N-barium hydroxide, were combined (filtrates A) and reserved for further examination (see below).

Esterification. The dry barium salts (6 g.) were boiled for 8 hours with 3% methyl-alcoholic hydrogen chloride (150 c.c.). The solution was cooled, neutralised with silver carbonate, filtered, and evaporated to dryness under slightly reduced pressure. The residue was dissolved in methyl alcohol, and inorganic salts precipitated by addition of excess of ether. Removal of the precipitate, followed by distillation of the solvent, gave a pale yellow liquid which crystallised spontaneously. Trituration with light petroleum, followed by recrystallisation from acetone or acetone–ether, gave methyl dihydroxyerythrosuccinate (*meso*tartrate) (0·52 g.), m. p. and mixed m. p. 114°. The crystals showed no rotation in methyl alcohol (*c*, 1·2) (Found: OMe, 34·8. Calc. for $C_6H_{10}O_6$: OMe, 34·8%).

Removal of the solvent from the mother-liquors after separation of the methyl dihydroxyerythrosuccinate gave a syrup which still contained a considerable amount of this ester, for nucleation readily caused crystallisation. Treatment of this residue with methyl-alcoholic ammonia for 3 days at − 5°, followed by removal of the solvent in a vacuum, gave a crystalline residue (0·6 g.) of dihydroxyerythrosuccinamide, m. p. 184° (decomp.) (after recrystallisation from aqueous alcohol). This amide had no appreciable rotation in water (*c*, 3·3) (Found: C, 32·7; H, 5·4; N, 19·0. Calc. for $C_4H_8O_4N_2$: C, 32·4; H, 5·4; N, 18·9%).

Examination of filtrates (A). The combined filtrates (A), see above, were treated with 0·3N-barium hydroxide until no further precipitate was produced. The precipitate was filtered off, suspended in water, and treated with a slight excess of N-sulphuric acid. The excess of acid was removed by addition of a little lead carbonate. The solution was filtered and treated with hydrogen sulphide. Removal of the precipitate by filtration and of the solvent by evaporation in a vacuum gave a syrup which crystallised spontaneously. Recrystallisation from ethyl alcohol gave mannosaccharodilactone (140 mg.), m. p. 196° (decomp.), $[\alpha]_D^{20°}$ +201° in water (*c*, 0·6). From the mother-liquor more dilactone (130 mg.) was obtained. Treatment of the syrup obtained from the mother-liquors gave mannosaccharodiamide (100 mg.), m. p. 204° (decomp.).

The Enol of 5-Keto-4-deoxymannosaccharo-3 : 6-lactone (II).—Mannosaccharodilactone (1 g.) was dissolved in the minimum amount of methyl alcohol and treated with 6 equivs. of 0·5N-sodium methoxide in methyl alcohol for 8—10 minutes at room temperature. Methyl-alcoholic hydrogen chloride was then added exactly to neutralise the sodium methoxide used. Removal of the sodium chloride by filtration, and of the solvent by evaporation under reduced pressure, gave a syrup which gradually crystallised. After recrystallisation from ethyl acetate or from ether–ethyl alcohol, the *enol* of *5-keto-4-deoxymannosaccharolactone monohydrate* had m. p. 82°, $[\alpha]_D^{18°}$ −48° (initial value in water; *c*, 1·2); − 34° (after 1 day); − 21·5° (2 days); − 7° (4 days); − 2·5° (5 days); + 2·0° (6 days); + 5° (7 days); + 9·5° (8 days); + 15° (11 days) (constant value). The hydrate immediately reacted with neutral potassium permanganate, bromine water, or chlorine water. It reduced Fehling's solution actively on warming (Found: C, 37·7; H, 5·0. $C_6H_8O_6,H_2O$ requires C, 37·5; H, 4·2%).

A freshly prepared aqueous solution of the enol (m. p. 82°) showed a band at λ 2290 A. (ε, 5000 approx.) (*c*, 5 mg. %), moving to λ 2650 A. (ε, 5000 approx.) on addition of alkali (Fig. 2). An aqueous solution of the substance which had undergone mutarotation still showed a band at λ 2290 A. but the intensity was much reduced. The enol reacted immediately at room temperature with 2 equivs. of sodium hydroxide (8·64 mg. required 8·85 c.c. of 0·01N-alkali for neutralisation, whence equiv., 97·5. $C_6H_8O_6$ requires equiv., 96).

The crystals of hydrated enol were treated with an excess of 0·01162N-iodine (30 c.c.) and N-sodium hydroxide (10 c.c.) at room temperature for 45 minutes. The solution was then acidified with N-sulphuric acid (10·1 c.c.), and excess of iodine titrated with 0·01N-sodium thiosulphate (4·53 mg. reacted with 14·0 c.c. of 0·01N-iodine, *i.e.*, 5·9 g.-atoms per g.-mol.). Small amounts of iodoform were formed.

When the monohydrate (m. p. 82°) was dried for 5 hours in a vacuum at 60° over phosphoric oxide and then for 3 hours at 100°, the water of crystallisation was eliminated and the m. p. rose to 142° (Found: loss, 9·9. $C_6H_8O_6,H_2O$ requires H_2O, 9·4%. Found, for anhydrous substance: C, 40·8; H, 4·0; equiv., 88. $C_6H_8O_6$ requires C, 41·4; H, 3·45; equiv., 87). In aqueous solution the *anhydrous* enol had $[\alpha]_D^{17°}$ −53° initial value (*c*, 1·8); − 43·5° (after 1 day); − 33° (2 days); − 17·5° (4 days); − 9° (5 days); − 2° (6 days); + 5·5° (7 days); + 14° (9 days); + 15·5° (10 days) (constant value). It reduced Fehling's solution actively on heating, decolorised bromine and permanganate, and immediately reacted with chlorine. The anhydrous 5-keto-4-deoxymannosaccharolactone showed a strong band at λ 2290 A. (ε, 4500 approx.; *c*, 5 mg. %), moving upon addition of sodium hydroxide to λ 2650 A. (ε, 4500 approx.; *c*,

5 mg. %) (Fig. 3). As in the case of the monohydrate (m. p. 82°), the mutarotation of the anhydrous material was accompanied by loss of the intensity of the band at λ 2290 A., the $\varepsilon_{max.}$ value at the equilibrium point being 1000 approx. (*c*, 25 mg. %).

In alkaline solution the anhydrous enol reacted with approximately 6 atomic proportions of iodine (6·08 mg. required 17·8 c.c. of 0·01162N-iodine. Calc. for 6 atomic proportions: 18·1 c.c.), a little iodoform being produced.

When titrated directly with chlorine water, with starch–iodide as an external indicator, approximately 4 atomic proportions of chlorine were consumed (11·66 mg. reacted with 9·4 c.c. of 0·0297N-chlorine; *i.e.*, 4·15 g.-atoms of Cl per g.-mol. of $C_6H_8O_6$). The acid was allowed to react for 5 minutes with an excess of chlorine water at room temperature. An excess of potassium iodide was then added to the solution, and the resulting iodine titrated with 0·01N-thiosulphate (11·07 mg. reacted with 8·7 c.c. 0·0297N-chlorine; *i.e.*, 4·05 g.-atoms of Cl per g.-mol. of the enol). Such aqueous solutions of the acid which have been treated with chlorine show no selective absorption.

Contrary to the behaviour with chlorine and bromine, both the enol of 5-keto-4-deoxymannosaccharolactone (m. p. 142°) and its hydrate (m. p. 82°) reacted with only small amounts of iodine.

Ozonisation of the Enol of 5-Keto-4-deoxymannosaccharo-3 : 6-lactone (II).—A solution of the enol (0·55 g.) in glacial acetic acid (25 c.c.) was treated as in previous examples with ozonised oxygen for 5 hours at room temperature. The rotation, initially $[\alpha]_D$ − 60°, had then become constant at + 7°. The solution was diluted with water, and acetic acid distilled off as before (p. 582). The residue was acidic, reduced Fehling's solution readily, and gave a positive oxalate test. A solution of the residue in water (15 c.c.) was neutralised by careful addition of barium hydroxide and treated with bromine (0·2 c.c.) at room temperature for 1 day. The solution was freed from bromine by aeration, neutralised with barium carbonate, and evaporated to dryness under reduced pressure. The dry residue of barium salts was boiled for 7 hours with 2% methyl-alcoholic hydrogen chloride (200 c.c.). Removal of the mineral acid with silver carbonate and of the solvent by distillation gave a syrupy residue which was purified by extraction with acetone–ether. The methyl oxalate, being readily volatile, is eliminated by the time this stage is reached. The syrup, which reacted faintly acid to Congo-red, was treated for 5 minutes in methyl alcohol (3 c.c.) with a slight excess of ethereal diazomethane. Removal of the solvent gave a neutral syrupy product (0·22 g.), which crystallised spontaneously. Recrystallisation from acetone gave methyl dihydroxyerythrosuccinate (*meso*tartrate), m. p. and mixed m. p. 114°. An aqueous solution (*c*, 2·8) of this ester showed no appreciable rotation (Found: C, 40·6; H, 5·65; OMe, 34·3. Calc. for $C_6H_{10}O_6$: C, 40·4; H, 5·6; OMe, 34·8%).

5-Methyl Δ⁴-Mannosaccharo-3 : 6-lactone 1-Methyl Ester (V).—A solution of the hydrate of the enol (II) (25 mg.) in methyl alcohol (2 c.c.) was titrated at 0° with a slight excess of ethereal diazomethane, the presence of the excess being indicated by the persistence of a yellow colour after 10 minutes. Removal of the solvent under reduced pressure gave the *ester* (V) as a syrup which, when purified by extraction with ether, had $[\alpha]_D^{18°}$ −30° in water (*c*, 0·9) (Found: OMe, 29·9. $C_8H_{10}O_6$ requires OMe, 30·7%). An aqueous solution of (V) showed a band at λ 2290 A. (ε, 5000 approx.; *c*, 5 mg. %) (Fig. 4) which disappeared upon addition of sodium hydroxide (tested at 20 mg. %).

Treatment of the anhydrous enol (II) (42 mg.; m. p. 142°) with ethereal diazomethane also gave this ester (V) (Found: OMe, 30·5%) (48 mg.), $[\alpha]_D^{18°}$ − 29·5° in water (*c*, 2·4), which had a band at λ 2290 A. in water (ε, 5000 approx.; *c*, 5 mg. %) (Fig. 4), disappearing upon addition of sodium hydroxide.

2 : 5-Dimethyl Δ⁴-Mannosaccharo-3 : 6-lactone 1-Methyl Ester (VI).—A solution of the enol (II) (0·52 g.) in methyl alcohol (5 c.c.) was allowed to react for 5 minutes with an excess of an ethereal solution of diazomethane. Concentration to dryness gave the syrupy ester (V). This was dissolved in acetone (3—5 c.c.) and allowed to react at 40—45° during 8 hours with silver oxide (5 g.) and methyl iodide (10 c.c.), the silver oxide being added in small portions at intervals of 1 hour. After recovery of the methyl iodide, the residue was exhaustively extracted with acetone and filtered. Removal of solvent from the combined acetone extracts gave a syrup which was subjected to two further treatments with silver oxide and methyl iodide to complete the methylation. Distillation gave 2 : 5-dimethyl Δ⁴-mannosaccharo-3 : 6-lactone 1-methyl ester (VI) (0·28 g.), b. p. (bath temp.) 175°/0·05 mm., $n_D^{20°}$ 1·4720, $[\alpha]_D^{18°}$ −36° in water (*c*, 1·2) (Found: OMe, 45·1. Calc. for $C_9H_{12}O_6$: OMe, 43·1%). Aqueous solutions of (VI) showed a strong band at λ 2290 A. (ε, 5000 approx.; *c*, 5 mg. %) (Fig. 4) which disappeared on addition of sodium hydroxide. On allowing a methyl-alcoholic solution of this syrupy form of (VI) to evaporate, there separated a very small amount of methyl 2 : 5-dimethoxymuconate, m. p. 140° alone or in admixture with a specimen previously prepared by direct methylation of mannosaccharodilactone (Haworth, Heslop, Salt, and Smith, *loc. cit.*). A solution of the crystals (m. p. 140°) in methyl alcohol was optically inactive. The presence of this compound (OMe, 54%) probably accounts for the high methoxyl value of the syrupy lactone ester (VI).

Slow evaporation of an aqueous solution of the syrup yielded crystals, m. p. 58°, $[\alpha]_D^{18°}$ −40° in water (*c*, 3·8) (after recrystallisation from ether). The pure ester (VI) had in aqueous solution a band at λ 2290 A. (ε, 6500 approx.; *c*, 5 mg. %) (Found: C, 49·95; H, 5·6; OMe, 42·7. Calc. for $C_9H_{12}O_6$: C, 50·0; H, 5·6; OMe, 43·1%). This crystalline ester failed to give a crystalline amide when treated with methyl-alcoholic ammonia.

2 : 5-Dimethyl Δ⁴-mannosaccharolactone was prepared by heating the crystalline ester (VI) (20 mg.) with 1 c.c. of N-sodium hydroxide for 30 minutes at 60°. The solution was cooled, treated with 10 c.c. of 0·1N-sulphuric acid, and evaporated to dryness under diminished pressure. Extraction of the residue with ethyl alcohol–ether gave an acidic product which failed to crystallise (Found: OMe, 29·9. $C_8H_{10}O_6$ requires OMe, 30·7%).

Ozonisation of 2 : 5-Dimethyl Δ⁴-Mannosaccharo-3 : 6-lactone 1-Methyl Ester (VI).—A solution of this ester (0·25 g.) in glacial acetic acid (10 c.c.) ($[\alpha]_D^{17°}$ −38·5°) was subjected to the action of a stream of ozonised oxygen for 3 hours at room temperature. The rotation was then constant ($[\alpha]_D^{17°}$ −2°). The solution was diluted with water, and evaporated to dryness under diminished pressure. The syrupy product obtained (0·21 g.) reacted acid to Congo-red; it reduced Fehling's solution actively on warming and gave a positive test for oxalic acid. It contained no glyoxylic acid, and none of this could be detected in the aqueous acetic acid distillate.

A solution of the syrup in water (8 c.c.) was treated with 0·3N-barium hydroxide until it reacted alkaline to phenolphthalein. The barium oxalate was filtered off, washed, and dried (0·1 g.). Evaporation of the filtrate and washings gave the barium salt of 3-methyl *d*-erythruronic acid (VII) as a pale yellow glassy solid (0·34 g.) which readily reduced Fehling's solution.

Formation of 2-Hydroxy-3-methoxy-d-erythrosuccinic Acid.—A solution of the barium salt (0·34 g.) obtained above, in water (10 c.c.), was oxidised with bromine (0·2 c.c.) for 24 hours at room temperature. The excess of bromine was removed by aeration, the solution neutralised with silver carbonate, treated with hydrogen sulphide, again filtered, and evaporated to dryness under reduced pressure. The residue was then boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (25 c.c.). The solution was cooled, neutralised with silver carbonate, filtered, and evaporated to dryness. The syrupy product, after purification by extraction with ether gave, upon distillation, methyl 3-hydroxy-2-methoxy-*l*-erythrosuccinate (IX) as a colourless, mobile liquid (90 mg.), b. p. (bath temp.) 120°/0·05 mm., $n_D^{17°}$ 1·4414 (Found: OMe, 48·3. Calc. for $C_7H_{12}O_6$: OMe, 48·5%).

When this ester (20 mg.) was treated with methyl-alcoholic methylamine for 24 hours at 0° it gave, after removal of the solvent, the crystalline bismethylamide (X) of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid, m. p. and mixed

m. p. 135°, $[\alpha]_D^{17°}$ +10·5° in water (*c*, 1·6) (after recrystallisation from ethyl acetate) (Found : OMe, 16·5. Calc. for $C_7H_{14}O_4N_2$: OMe, 16·2%).

The Methyl Ester of the Enol of 3-*Keto*-4-*deoxymannosaccharolactone*.—Mannosaccharodilactone (2 g.) in dry methyl alcohol (10 c.c.) was allowed to react for 3—5 minutes with 3 equivs. of 0·5N-sodium methoxide in methyl alcohol (69 c.c.) at room temperature. An intense yellow colour developed immediately upon addition of the sodium methoxide. The methoxide was then neutralised by the addition of the calculated amount of 5% methyl-alcoholic hydrogen chloride, and the solution filtered. Evaporation of the filtrate at 40° under reduced pressure gave a product which was freed from inorganic impurity by extraction with alcohol containing a little ether. Removal of the solvent yielded a syrup which partly crystallised. The crystals were separated by tiling, and after purification by recrystallisation from ethyl alcohol–ether the *methyl* ester of the enol of 5-keto-4-deoxymannosaccharolactone (200 mg.) had m. p. 111°, $[\alpha]_D^{17°}$ −41·3° initial value in water (*c*, 0·6) ; − 15° (after 20 hours) ; + 8° (70 hrs.) ; constant for further 30 hrs. (Found : OMe, 15·4. $C_7H_8O_6$ requires OMe, 16·5%). Aqueous solutions of this compound showed a selective absorption band at λ 2290 A. (ε, 5000 approx. ; *c*, 4 mg. %), moving to λ 2650 A. (ε, 4500 approx. ; *c*, 6 mg. %) on addition of sodium hydroxide. Aqueous solutions of the crystals react acid to Congo-red, reduce hot Fehling's solution, and decolorise acid potassium permanganate in the cold. The compound can be titrated directly with approximately 1 equiv. of sodium hydroxide at room temperature (9·502 mg. required 5·4 c.c. of 0·01N-sodium hydroxide. Calc. for 1 equiv. : 5·06 c.c.). On keeping this solution with an excess of 0·01N-sodium hydroxide a further 5·24 c.c. (determined by back titration) were taken up.

When the crystals (m. p. 111°) (9·261 mg.) were treated with 3 c.c. of 0·3N-baryta for 1 hour at 50° the methoxyl group was eliminated, as shown by a nil Zeisel determination, carried out upon the dry residue obtained by evaporation of the solution (neutralised by carbon dioxide) under reduced pressure. This suggested the esteric character of the single methoxyl group.

A solution of the crystals (12·02 mg.) in water (1 c.c.) was treated with 25 c.c. of 0·02N-chlorine water for 5 minutes. Potassium iodide was then added, and the liberated iodine titrated with 0·02N-thiosulphate ; 14·5 c.c. of 0·02N-chlorine were used (Calc. for 4Cl : 12·8 c.c.).

Two experiments were carried out in which the crystals (m. p. 111°) were treated with 0·01N-iodine in N-sodium hydroxide (10 c.c.) at room temperature for 45 minutes : 9·872 and 3·899 mg. reacted with 34·0 and 13·6 c.c., respectively, of 0·01N-iodine (Calc. for 6I : 31·5, 12·5 c.c., respectively).

Upon treatment of the ester (m. p. 111° ; 25 mg.) in methyl alcohol (3 c.c.) with excess of ethereal diazomethane for 10 minutes at 0°, followed by removal of the solvent, there was obtained a syrup (purified by extraction with ether) which had $[\alpha]_D^{17°}$ −29·5° in water (*c*, 1·0) (Found : OMe, 30·5. $C_8H_{10}O_6$ requires OMe, 30·7%). An aqueous solution of this *dimethyl* derivative had a band at λ 2290 A. (ε, 6000 approx. ; *c*, 6 mg. %) which disappeared upon addition of sodium hydroxide. The dimethyl derivative was still unsaturated, for it reacted with chlorine and with bromine. It did not reduce Fehling's solution.

Several attempts to repeat the preparation of the compound, m. p. 111°, failed, the crystalline enol of 5-keto-4-deoxymannosaccharo-3 : 6-lactone being obtained instead. The formation of the compound, m. p. 111°, was probably due to the use of a slight excess of methyl-alcoholic hydrogen chloride which was added to neutralise the sodium methoxide used in the isomerisation of the dilactone.

Treatment of the Enol of 5-*Keto*-4-*deoxymannosaccharolactone* (II) *with Chlorine*.—A solution of the crystalline enol (0·3 g.) in water (10 c.c.) was allowed to react with 0·19N-chlorine water (100 c.c.) for 10 minutes at room temperature. After removal of the excess of the chlorine by aeration, the solution (which now showed no selective absorption) was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure at 40°. The residue was boiled for 7 hours with 2% methyl-alcoholic hydrogen chloride (150 c.c.). Removal of mineral acid with barium carbonate, followed by filtration and elimination of solvent under reduced pressure, gave a syrupy product which reacted acid to Congo-red. A second esterification with 2% methyl-alcoholic hydrogen chloride still failed to effect esterification, and the product reacted acid to Congo-red. The product was therefore dissolved in methyl alcohol (10 c.c.) and treated with a slight excess of an ethereal solution of diazomethane. Immediate concentration of the solution yielded a partly crystalline product which, after recrystallisation from water, had m. p. 127° (0·15 g.), $[\alpha]_D^{20°}$ −13° in ethyl alcohol (*c*, 1·2). This *methyl* 4 : 5-*dichloro*-2 : 3-*dihydroxy*-5-*methoxyadipate* (XVII) did not reduce Fehling's solution or react with bromine. Aqueous solutions of it were transparent to ultra-violet light (Found : C, 35·7 ; H, 4·2 ; OMe, 30·0 ; Cl, 25·5 ; equiv., by heating at 60° with 0·02N-sodium hydroxide, 146. $C_9H_{14}O_7Cl_2$ requires C, 35·4 ; H, 4·6 ; OMe, 30·5 ; Cl, 23·3% ; equiv., 152·5).

Removal of the solvent from the mother-liquors after isolation of the dichloro-ester gave a syrupy product which, although transparent to ultra-violet light, was strongly reducing to Fehling's solution.

The crystalline dichloro-ester (XVII) (50 mg.) (m. p. 127°) was warmed at 60° for 45 minutes with 0·1N-sodium hydroxide (4 c.c.) and then neutralised with 4 c.c. of 0·1N-sulphuric acid. The solution was concentrated to dryness, and the residue extracted with ether–ethyl alcohol. This gave the *dichloro-acid*, a liquid (42 mg.) which reacted strongly acid to Congo-red (Found : OMe, 10·9. $C_7H_{10}O_7Cl_2$ requires OMe, 11·2%).

Treatment of the dichloro-ester (XVII) (40 mg.) with methyl-alcoholic ammonia at − 5° for 3 days, followed by removal of the solvent in a vacuum, gave a crystalline monoamide (XVIII) (25 mg.), m. p. 197°, $[\alpha]_D^{19°}$ −20° in water (*c*, 1·8) (after one crystallisation from acetone and one from water), which showed a positive Weerman reaction.

Three methylations of the dichloro-ester (90 mg.) (m. p. 127°) with silver oxide (2—3 g.) and methyl iodide (3 c.c.), acetone (1 c.c.) being added to aid solution, effected the introduction of one additional methoxyl group, giving *methyl* 4 : 5-*dichloro*-2 (or 3)-*hydroxy*-3 (or 2) : 5-*dimethoxyadipate*, m. p. 116°, $[\alpha]_D^{18°}$ +15° in methyl alcohol (*c*, 1·6) (Found : C, 38·2 ; H, 4·2 ; OMe, 39·1 ; Cl, 22·35. $C_{10}H_{16}O_7Cl_2$ requires C, 37·6 ; H, 5·0 ; OMe, 38·9 ; Cl, 22·3%).

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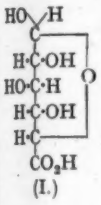
157. *Glucurone.*

By F. Smith.

Treatment of glucurone with silver oxide and methyl iodide results in the formation of an analogue of ascorbic acid, 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (X) (Schmidt, Dippold, and Zeiser, *Ber.*, 1937, **70**, 2402 ; Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 450 ; this vol., p. 510). This substance, first isolated but not characterised by Pryde and Williams (*Biochem. J.*, 1933, **27**, 1205), was accompanied by a crystalline trimethyl glucurone (IV). The latter is shown to be a 2 : 5-dimethyl methylglucofururonoside by the fact that it can be converted into the crystalline diamide (VIII) of 2 : 5-dimethyl glucosaccharic acid and also into 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester.

THE trimethyl glucurone (IV) can only be obtained on methylating glucurone (Pryde and Williams, *loc. cit.*) by means of silver oxide and methyl iodide if care is taken to avoid oxidation of the reducing group, probably rendered more active by the dicyclic system present in glucurone; some oxidation usually occurs and there is formed 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (X). When the glucurone was thus methylated at room temperture until the reducing group was methylated, a yield of 34% of trimethyl glucurone was obtained, and later, by the use of a still lower temperature in the initial stages of the methylation, Reeves (*J. Amer. Chem. Soc.*, 1940, **62**, 1616) obtained (IV) in a yield of 50%.

Since free sugars exist in the pyranose form, it seemed reasonable to expect that glucuronic acid would possess a six-atom ring as in (I), and that lactonisation would effect elimination of water between C_3 and C_6 (a lactone ring between C_2 and C_6 is stereochemically impossible) and afford glucurone with the structure (II). The other possible structure for glucurone (III), in which there is a 5-atom furanose ring and a 5-atom 3 : 6-lactone ring, had been considered (Smith, *loc. cit.*, 1938) but not deemed probable. It was therefore surprising to find that glucurone in the form of its trimethyl derivative contained two 5-atom rings. Subsequently, however, when investigations into similarly constituted compounds, such as the methylglycosides of 3 : 6-anhydroglucose, revealed that those derivatives containing two 5-atom rings were more stable than those with a 5- and a 6-atom ring (Haworth, Owen, and Smith, J., 1941, 88), the formulation of trimethyl glucurone as a substance with two 5-atom rings as in (III) became explicable.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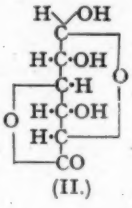
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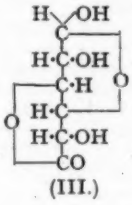
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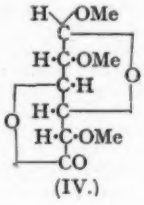
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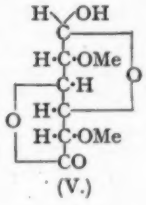
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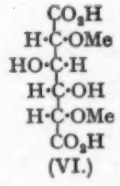
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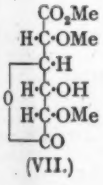
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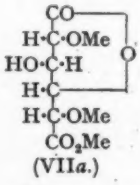
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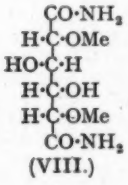
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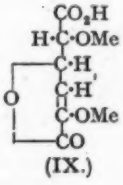
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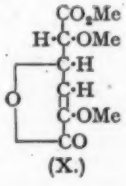
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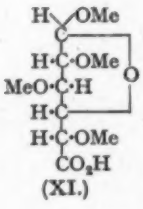
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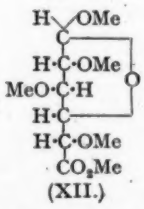
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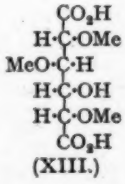
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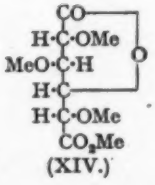
(XIV.)

The experimental basis upon which the structure (IV) is assigned to the crystalline trimethyl glucurone is as follows. The substance readily undergoes hydrolysis with dilute acid to give a dimethyl derivative of glucuronic acid (V). Oxidation of the latter with bromine may be considered to give the corresponding dimethyl glucosaccharic acid (VI), from which by means of methyl-alcoholic hydrogen chloride there were produced a dimethyl glucosaccharolactone methyl ester (VII, or VII*a*) and crystalline 2 : 5-dimethyl Δ^4-glucosaccharolactone (IX). The latter was identified by comparison with specimens previously made and characterised, and by its conversion into the methyl ester (X) with ethereal diazomethane (Smith, this vol., p. 515). The identification of (IX) strongly suggested that the two methyl groups in the lactone ester (VII, or VII*a*), and therefore in the trimethyl glucurone (IV), were located at C_2 and C_5. However, in view of the peculiar nature and formation of (X) from glucurone, this was not taken as good evidence for the determination of the structure of the trimethyl glucurone (cf. Reeves, *loc. cit.*), but the negative Weerman test (*Rec. Trav. chim.*, 1917, **36**, 16) displayed by the *diamide* (VIII) derived from the dimethyl glucosaccharolactone methyl ester (VII, or VII*a*) was taken as conclusive proof of the existence of the two methyl groups at C_2 and C_5 in trimethyl glucurone (IV). This clearly eliminated the structure (II) for glucurone, since this would give rise to a 2 : 4-dimethyl derivative of glucosaccharic acid. Moreover, since it is highly unlikely from stereochemical considerations that two 4-atom rings (a 1 : 3- and a 4 : 6-ring) could exist in glucurone and its trimethyl derivative, the location of the C_2 and C_5 methyl groups strongly supported the structure (III) for glucurone and (IV) for the crystalline trimethyl derivative.

Final proof of this was forthcoming from the fact that treatment of (IV) with sodium hydroxide and methyl sulphate, reagents which may open lactone rings and methylate any hydroxyl group set free, resulted in the formation of trimethyl methylglucofururonoside (XI), which was smoothly converted into the corresponding

methyl ester (XII) by means of ethereal diazomethane. Had this methyl ester (XII) contained any 2 : 3 : 4-trimethyl α-methylglucopyruronoside, it would easily have been recognised in the formation of its crystalline amide (Smith, J., 1939, 1724); when it was treated with methyl-alcoholic ammonia, however, none was detected. Oxidation of (XII) with concentrated nitric acid afforded a trimethyl glucosaccharic acid (XIII) which, by esterification and distillation, gave the characteristic crystalline 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester (XIV) (Smith, this vol., p. 571). The isolation of the latter having methyl groups at 2, 3, and 5 shows that, during the treatment of trimethyl glucurone (IV) with methyl sulphate and sodium hydroxide, a methyl group was introduced at C_3. Therefore, the lactone ring in trimethyl glucurone must engage C_3 and C_6, and hence the second ring of (IV) must join C_1 and C_4. Since the crystalline trimethyl glucurone (IV) shows a high positive rotation (+179°), it is believed to be an α-glycoside and hence it is designated as the 3 : 6-monolactone of 2 : 5-dimethyl α-methylglucofururonoside. The presence of two 5-atom rings in trimethyl glucurone (IV) thus being proved, it seems highly probable that this is true also for glucurone itself (III), in which case glucurone would appear to be one of the few furanose sugars existing in the free crystalline state (compare 3 : 6-anhydroglucose).

Experimental.

2 : 5-Dimethyl α-Methylglucofururonoside 3 : 6-Lactone (Trimethyl Glucurone) (IV).—Finely powdered crystalline glucurone (1·8 g.) in dry methyl alcohol (10 c.c.) and methyl iodide (2 c.c.) was treated with silver oxide (1 g.) at 15°. The mixture was shaken from time to time and the temperature was gradually raised in 1 hour to 27°, at which point methyl iodide (2 c.c.) was added. After 2½ hours the temperature had reached 35°; portions of methyl iodide (2 c.c.) and silver oxide (2 g.) were added then and again after a further hour at 35°, these additions being repeated after another 1½ hours, during which the temperature had been slowly increased to 40°. The operation was completed by heating for a further 3½ hours at 40°. The reaction mixture was filtered, and the residue washed well with hot acetone. Removal of the solvent from the combined filtrate and washings gave a pale yellow syrup which was subjected to further methylation by boiling with methyl iodide (10 c.c.) in the presence of silver oxide (5 g.) in the normal manner. The product, isolated by means of acetone, crystallised spontaneously. Purification by recrystallisation from ethyl alcohol–ether gave crystalline trimethyl glucurone, m. p. 132—133°, $[\alpha]_D^{20°}$ +179° in water (*c*, 0·4) (initial value, solution neutral to litmus); +149° (44 days; solution now acid to litmus); +134° (139 days). The substance does not reduce Fehling's solution. Retreatment of the syrup from the mother-liquors with silver oxide and methyl iodide gave a further small yield of crystalline material upon nucleation. The total yield of trimethyl glucurone was 0·75 g. (34%) (Found : C, 49·5; H, 6·5; OMe, 42·5. Calc. for $C_9H_{14}O_6$: C, 49·5; H, 6·5; OMe, 42·7%). Since this work was completed, Reeves (*loc. cit.*) has obtained (IV) in a yield of 50%.

Treatment of this trimethyl glucurone (20 mg.) with methyl-alcoholic ammonia for 24 hours at −5° gave the *amide* of 2 : 5-dimethyl methylglucofururonoside in good yield, m. p. 121° (after recrystallisation from ethyl alcohol–ether–light petroleum), $[\alpha]_D^{16°}$ +149·5° in water (*c*, 1·2) (Found : C, 46·4; H, 8·0; N, 6·1; OMe, 39·1. $C_9H_{17}O_6N$ requires C, 46·0; H, 7·3; N, 6·0; OMe, 39·6%).

Distillation of the syrup obtained from the mother-liquors after separation of trimethyl glucurone gave : Fraction I, 0·56 g., b. p. 120—125° (bath temp.)/0·02 mm., $n_D^{19°}$ 1·4470 (Found : OMe, 55·6. Calc. for the methyl ester of 2 : 3 : 5-trimethyl methylglucofururonoside : OMe, 58·7%); fraction II, 0·7 g., b. p. 140—160° (bath temp.)/0·02 mm., $n_D^{20°}$ 1·4580–1·4680, which crystallised slowly on standing. Trituration of the syrupy crystalline mass with ether–ethyl alcohol to remove the syrup, followed by recrystallisation from ethyl alcohol–ether, gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (X), m. p. and mixed m. p. 89°.

Care must be exercised during the initial stages of the methylation of glucurone with Purdie's reagents, otherwise oxidation of the reducing group readily proceeds and the only crystalline product of the reaction is the unsaturated 2 : 5-dimethyl Δ^4-glucosaccharolactone 1-methyl ester.

Hydrolysis of the Monolactone (IV).—A solution of the crystalline lactone (0·92 g.) in N-sulphuric acid (20 c.c.) was heated on the boiling water-bath for 2 hours : $[\alpha]_D$ +165° (initial value); +62° (1 hr.); constant for a further hour. The solution, which at this stage reduced boiling Fehling's solution, was neutralised with barium carbonate, treated with a little charcoal, and filtered. After the residue had been washed with hot water, the filtrate was evaporated to dryness under diminished pressure. The barium 2 : 5-dimethyl glucuronate was obtained as a glassy solid which reduced Fehling's solution.

Oxidation. A solution of the glassy residue in water (15 c.c.) was treated with bromine (1 c.c.) at room temperature for 3 days and then no longer reduced Fehling's solution. Excess of bromine was removed by aeration. The solution was neutralised with silver oxide, filtered, and the filtrate was freed from silver ions by hydrogen sulphide. The solution was again filtered, and evaporated to dryness under reduced pressure, giving an acid product which also contained barium.

Esterification. The residue obtained from the previous experiment was boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (50 c.c.). The solution was cooled, neutralised with silver carbonate, filtered, and evaporated to dryness. Purification of the syrupy product by extraction with ether followed by distillation gave : Fraction I (0·3 g.), b. p. 185° (bath temp.)/0·02 mm., $n_D^{12°}$ 1·4700; fraction II (0·36 g.), b. p. 220° (bath temp.)/0·02 mm., which crystallised spontaneously.

Examination of fraction I. An aqueous solution of the syrupy product gave a slightly acid reaction to litmus; it had $[\alpha]_D^{16°}$ +56° in water (*c*, 0·5) (initial value); +37° (7 hrs.); +34° (22 hrs.) [Found : OMe, 41·6. Calc. for $C_9H_{14}O_7$ (2 : 5-dimethyl glucosaccharo-3 : 6-lactone 1-methyl ester) : OMe, 39·8%]. The rest of the product was subjected to treatment with methyl-alcoholic ammonia at −5° for 2 days. The liquid was decanted from the crystals and evaporated to dryness in a vacuum. Recrystallisation of the combined crystalline products from ethyl alcohol gave the *diamide* (VIII) of 2 : 5-dimethyl glucosaccharic acid, m. p. 175°, $[\alpha]_D^{22°}$ +17° in water (*c*, 1·6) (Found : C, 41·1; H, 6·9; N, 11·5; OMe, 26·0. $C_8H_{16}O_6N_2$ requires C, 40·7; H, 6·8; N, 11·9; OMe, 26·3%). A Weerman test on this amide (20 mg.) was negative, a control test on gluconamide (20 mg.) being positive.

Examination of fraction II. Isolation of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone. The solid distillate, after two recrystallisations from acetone–ether–light petroleum, had m. p. 171° alone or in admixture with a specimen of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone previously prepared from silver saccharate, saccharo-3 : 6-lactone, saccharo-1 : 4-lactone, and saccharo-1 : 5-3 : 6-dilactone (Smith, this vol., p. 510). An aqueous solution of it reacted acid to Congo-red paper and showed selective absorption with the head of the band at 2290 A. (ε, 8000 approx.) (*c*, 3 mg. per 100 c.c.); it decolourised alkaline potassium permanganate in the cold but did not reduce Fehling's solution on boiling. The 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone had $[\alpha]_D^{18°}$ +76° in methyl alcohol (*c*, 0·7); $[\alpha]_D^{18°}$ +72° in water (*c*, 2·6) (initial value); equiv., 200 (by direct titration in the cold); 98 (after warming with 0·01N-sodium hydroxide) (Found : C, 47·7; H, 5·05; OMe, 31·2. Calc. for $C_6H_{10}O_6$: C, 47·5; H, 5·0; OMe, 30·7%).

Treatment of a solution of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone (10 mg.) in methyl alcohol (1 c.c.) with a slight excess of ethereal diazomethane, followed by immediate removal of the solvent, gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m. p. and mixed m. p. 89°.

Methylation of the 3 : 6-*Monolactone of* 2 : 5-*Dimethyl Methylglucofururonoside with Methyl Sulphate.*—The crystalline lactone (0·3 g.), dissolved in acetone (10 c.c.), was treated with methyl sulphate (5 c.c.) and 30% sodium hydroxide solution (15 c.c.). The reagents were added dropwise during 1½ hours to the reaction mixture, which was well stirred and maintained at 40°. After another ½ hr.'s heating, the methylation mixture was cooled in ice, acidified with dilute sulphuric acid, and filtered to remove sodium sulphate, which was washed with chloroform, the washings being collected in the same filter flask as the aqueous filtrate. The chloroform layer was separated, and the aqueous layer extracted four times with chloroform. The chloroform extracts were combined, washed twice with a saturated solution of sodium sulphate, and then dried over anhydrous magnesium sulphate. The solution was filtered, and evaporated under slightly reduced pressure at 35°. The pale yellow, syrupy product thus obtained (0·3 g.) reacted acid to Congo-red paper. It was subjected to methylation by 6 hours' boiling with methyl iodide (5 c.c.) in the presence of silver oxide (2 g.). Isolation of the product by means of acetone, followed by removal of the solvent, gave the methyl ester of 2 : 3 : 5-trimethyl methylglucofururonoside (XII), which distilled as a colourless, mobile liquid (0·27 g.), b. p. 120° (bath temp.)/0·03 mm., $n_D^{16°}$ 1·4480, $[\alpha]_D^{18°}$ +122° in water (*c*, 0·7) (Found: OMe, 57·0; equiv., by heating with 0·01N-NaOH for 1 hour at 60°, 260. $C_{11}H_{20}O_7$ requires OMe, 58·7%; equiv., 264). This ester failed to give a crystalline amide upon treatment with methylalcoholic ammonia for 2 days at −5°.

Oxidation of the Methyl Ester of 2 : 3 : 5-*Trimethyl Methylglucofururonoside with Nitric Acid.*—The syrupy ester (0·2 g.) obtained above was heated with nitric acid (3 c.c.; *d* 1·42) for ½ hour at 60° and for 1½ hours at 90°, oxidation then appearing to be complete. The solution was diluted with water and evaporated under diminished pressure, water being added from time to time to facilitate removal of nitric acid. The last traces of the latter were removed by addition and distillation of methyl alcohol under reduced pressure. The dry, acid, syrupy residue was then esterified by dissolving it in methyl alcohol (5 c.c.) and adding a slight excess of ethereal diazomethane. Removal of solvent gave a colourless liquid, which crystallised spontaneously. It was purified by distillation in a high vacuum. Recrystallisation from ether gave 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester, m. p. and mixed m. p. 78—79°, $[\alpha]_D^{18°}$ −10° in water (*c*, 3·2) (Found: C, 48·6; H, 6·1; OMe, 50·15. Calc. for $C_{10}H_{16}O_7$: C, 48·4; H, 6·45; OMe, 50·0%).

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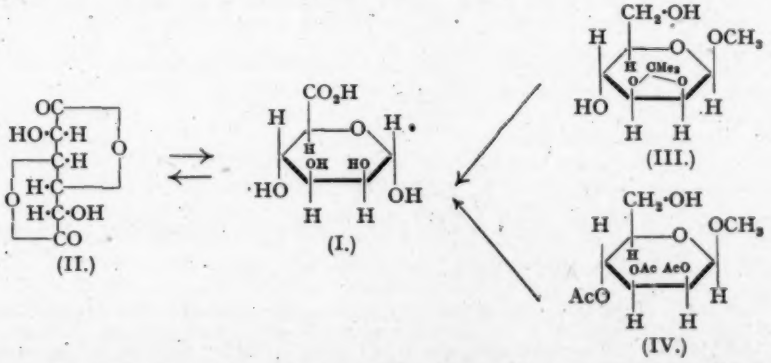
158. *Synthesis of Uronic Acids. Part III.* d-*Mannuronic Acid.*

By M. Stacey and P. I. Wilson.

A synthesis of crystalline *β-d*-mannuronolactone in good yield from mannose is described. The stages involved are the following: mannose ⟶ α-methylmannoside ⟶ 2 : 3 : 4-triacetyl 6-trityl α-methylmannoside ⟶ 2 : 3 : 4-triacetyl α-methylmannoside ⟶ 2 : 3 : 4-*triacetyl α-methylmannuronoside* ⟶ *α-methylmannuronoside lactone* ⟶ *β-d*-mannuronolactone.

Mannuronic acid (I) is the sole identified constituent unit of the important sea-weed product alginic acid (Nelson and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1914; 1930, **52**, 2130; Hirst, Jones, and Osman Jones, J., 1939, 1880). Two methods for its synthesis have been devised. The first (Shoeffel and Link, *J. Biol. Chem.*, 1933, **100**, 40) was based on Fischer and Piloty's method (*Ber.*, 1891, **24**, 521) and involved the reduction of mannosaccharodilactone (II) with sodium amalgam. In the second (Ault, Haworth, and Hirst, J., 1935, 517), 2 : 3-monoacetone α-methylmannoside (III) was oxidised at C_6 with alkaline potassium permanganate to give monoacetone α-methylmannuronoside, which after acid hydrolysis gave mannuronic acid in the form of its crystalline lactone.



In our hands repetition of both of these methods gave products which were difficult to crystallise, so that a third route (Stacey, J., 1939, 1529) was explored. This method utilised 2 : 3 : 4-triacetyl α-methylmannoside (IV) (cf. Watters, Hockett, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1529) as initial material which was obtained in good yield by the first three processes shown in the summary (above).

Oxidation of the triacetyl compound at C_6 was readily effected with potassium permanganate in acetone–acetic acid solution, giving syrupy 2 : 3 : 4-triacetyl α-methylmannuronic acid (characterised by conversion into *α-methylmannuronoside lactone*, m. p. 186°, $[\alpha]_D$ +80°), which was deacetylated with aqueous barium hydroxide, and then the glucosidic group was hydrolysed by N/2-sulphuric acid. The product readily crystallised in the

form of β-*d*-mannuronolactone, identical with specimens synthesised by both of the previous methods mentioned above. Further amounts were obtained by slow crystallisation of mother-liquor products after lactonisation.

Oxidation with bromine water of the syrupy mother-liquor product from the crystallisation of mannuronolactone gave mannosaccharodilactone (II) in 65% yield. In view of the fact that bromine water is known to oxidise reducing sugars only at C_1, it is clear that this syrupy product was a mixture of *d*-mannuronic acid with its lactone. Hence the yield in the conversion of (IV) into (I) was reasonably good.

Experimental

2 : 3 : 4-Triacetyl 6-Trityl α-Methylmannoside.—This was prepared in theoretical yield by the method of Smith, Stacey, and Wilson (this vol., p. 131) and showed $[\alpha]_D^{20°}$ +42·2° in chloroform (*c*, 1·0), m. p. 128° (cf. Watters, Hockett, and Hudson, *loc. cit.*).

2 : 3 : 4-Triacetyl α-Methylmannoside.—A solution of the 6-trityl compound in glacial acetic acid was detritylated by Helferich and Klein's method (*Annalen*, 1926, **450**, 219), and the product recrystallised from acetone–ether. It was obtained in 85% yield; m. p. 97°, $[\alpha]_D^{20°}$ +55° in chloroform (*c*, 1·0) (Found: OMe, 9·7. Calc. for $C_{13}H_{20}O_9$: OMe, 9·7%).

Oxidation of 2 : 3 : 4-Triacetyl α-Methylmannoside.—The foregoing compound (10 g.) was dissolved in glacial acetic acid (100 c.c.), potassium permanganate (2·5 g.) in acetone (100 c.c.) and water (25 c.c.) was added, and the mixture gently stirred at room temperature. More permanganate (8 g.) was added in small quantities over a period of 2 days. Acetone (100 c.c.) and ether (200 c.c.) were added to the mixture, and the precipitate of manganese dioxide separated (centrifuge) and washed well with acetone–ether. The combined supernatant liquors were evaporated under diminished pressure to a brown syrup, which was dissolved in chloroform (100 c.c.) and washed with dilute sulphuric acid and then with water. The chloroform solution was dried over anhydrous magnesium sulphate, and the solvent removed, giving mainly *2 : 3 : 4-triacetyl α-methylmannuronoside* as a thick yellow syrup (7·8 g.), $[\alpha]_D^{20°}$ +41° in chloroform (*c*, 1·05) (Found: OMe, 9·0. $C_{13}H_{18}O_{10}$ requires OMe, 9·3%). The syrup gave a strongly positive naphtharesorcin test for uronic acid.

α-Methylmannuronoside Lactone.—(*a*) 2 : 3 : 4-Triacetyl α-methylmannuronoside (1·0 g.) was dissolved in methyl alcohol (30 c.c.) containing anhydrous hydrochloric acid (1%), and the solution boiled for 3 hours ($[\alpha]_D^{20°}$ +52° ⟶ +38°), neutralised with silver carbonate, filtered, and concentrated. The residual syrup (0·6 g.) was dissolved in ether, the solution filtered, and the solvent again removed. The product (0·5 g.) slowly crystallised. After being kept for several weeks it was stirred with a small amount of absolute methyl alcohol and the solution filtered. The residual *α-methylmannuronoside lactone*, recrystallised from methyl alcohol, had m. p. 186°, $[\alpha]_D^{20°}$ +80° (*c*, 1·1 in water) (Found: C, 43·9; H, 5·3; OMe, 16·7. $C_7H_{10}O_6$ requires C, 44·2; H, 5·3; OMe, 16·3%).

(*b*) 2 : 3 : 4-Triacetyl α-methylmannuronoside (3·8 g.) was dissolved in acetone (30 c.c.), and saturated aqueous barium hydroxide added until the solution was alkaline to phenolphthalein. It was kept for six hours at room temperature, and the barium then removed by quantitative addition of N-sulphuric acid. Evaporation of the solvents gave α-methylmannuronoside as a colourless, viscid syrup (2·1 g.), $[\alpha]_D^{20°}$ +70° in water (*c*, 1·0) (Found: OMe, 16·0%).

β-d-Mannuronolactone.—The mannuronoside syrup (2·1 g.) was dissolved in N/2-sulphuric acid (250 c.c.), the solution heated at 100° for 3½ hours ($[\alpha]_D^{20°}$ +74° ⟶ +17°; equilibrium value), neutralised with aqueous barium hydroxide, and the precipitate of barium sulphate removed (centrifuge) and washed well with water. The supernatant liquors were evaporated under diminished pressure to 50 c.c., and the barium mannuronate precipitated as a white powder by addition of ethyl alcohol (4 vols.). The barium salt was converted into the lead salt, from which mannuronic acid was obtained in solution by means of hydrogen sulphide. Removal of solvent gave mannuronic acid as a colourless syrup (1·5 g.), strongly acid to Congo-red indicator. After intensive drying at 70° in a vacuum, the syrup was dissolved in a small amount of ethyl alcohol and ether was added. Crystallisation was rapid and the product, recrystallised from ethyl alcohol containing glacial acetic acid, had m. p. and mixed m. p. 143—144° with specimens of mannuronolactone supplied by Professor K. P. Link and by Professor W. N. Haworth, F.R.S.; $[\alpha]_D^{21°}$ +50° ⟶ +94° in 30 minutes (Found: C, 41·2; H, 4·7. Calc. for $C_6H_8O_6$: C, 40·9; H, 4·6%).

Mannosaccharodilactone.—Evaporation of the mother-liquors from the crystallisation of mannuronolactone gave syrupy products from which mannuronolactone slowly crystallised as broad plates. A syrupy sample (0·20 g.) was oxidised in the usual way with bromine water at 40° over a period of three days, and from the solution mannosaccharodilactone (0·14 g.) (m. p. 190°, decomp.), identical with an authentic specimen, was isolated.

The authors thank Professor W. N. Haworth, F.R.S., for his interest in this work, and Mrs. V. Gilbert for practical assistance.

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159. *The Influence of Inert Gases on the Photodecomposition of Gaseous Acetone.*

By T. Iredale and L. E. Lyons.

A study has been made of the influence of the inert gases carbon dioxide and nitrogen at pressures near to atmospheric on the photodecomposition of gaseous acetone at room temperatures in light of wave-length 2400—3100 A. The yield of carbon monoxide was found to be increased, no detectable amounts of diacetyl were formed, and the ratio C_2H_6/CO approached unity. Reasons are given for this change in behaviour of the photodecomposing acetone.

The photodecomposition of gaseous acetone has been the subject of many investigations. The main products are ethane, carbon monoxide, and diacetyl, with increasing amounts of methane as the temperature is raised (Damon and Daniels, *J. Amer. Chem. Soc.*, 1933, **55**, 2363; Norrish, Crone, and Saltmarsh, J., 1934, 1456; Barak and Style, *Nature*, 1935, **135**, 307; Spence and Wild, J., 1937, 352; 1941, 590; Herr and Noyes, *J. Amer. Chem. Soc.*, 1940, **62**, 2052). The different proportions of the products, and, in particular, the ratio C_2H_6/CO, depend very much on the wave-length of the light used, the intensity of the light, and the pressure

of the acetone. The absorption spectrum of acetone is not an easy one to interpret, but definite regions have now been distinguished, and certain consequences to the molecule on absorption of light in these regions have been assumed (Baur and Rebmann, *Helv. Chim. Acta*, 1922, **5**, 828; Scheibe, Povenz, and Linstrom, *Z. physikal. Chem.*, 1933, *B*, **20**, 297; Noyes, Duncan, and Manning, *J. Chem. Physics*, 1934, **2**, 717; Norrish, Crone, and Saltmarsh, *loc. cit.*). The " banded " region in the neighbourhood of 3130 A. gives rise to excited molecules, as likewise does another banded region on the borderland of the quartz ultra-violet, 1800—1950 A. (Howe and Noyes, *J. Amer. Chem. Soc.*, 1936, **58**, 1404). Light absorbed in the " continuum " region, 2500—3000 A., breaks the molecule into radicals: $CH_3{\cdot}CO{\cdot}CH_3 + h\nu = CH_3 + CO{\cdot}CH_3$. The acetyl radical $CH_3{\cdot}CO$, however, is not very stable, and sometimes contains enough internal energy, on rearrangement, to break it up into CH_3 and CO. It may lose this energy by collision with other molecules, but at higher temperatures there is a greater probability of its acquiring more energy by collisions to make it again unstable. Low temperatures and high light intensities therefore favour the detection of this radical, which can combine with itself to give diacetyl: $2CH_3{\cdot}CO = (CH_3{\cdot}CO)_2$. A high value of the ratio C_2H_6/CO indicates the formation of relatively large amounts of diacetyl, and a low value small amounts. Ultimately, when C_2H_6/CO becomes unity, no diacetyl is formed.

It seems that the excited molecules formed in the 3130 A. region can also break up into CH_3 and $CO{\cdot}CH_3$, although not immediately, according to the assumptions of Spence and Wild (1941, *loc. cit.*). Diacetyl is therefore formed in this region as well as in the continuum. The over-all results obtained in the " banded " region are somewhat different from those in the " continuum," and rather different results are obtained again when " mixed light," *i.e.*, λλ 2500—3100 A., is used. These matters are not discussed here, but such of them are mentioned later as have a bearing on our discovery that in the presence of such inert gases as carbon dioxide and nitrogen at moderately high pressures, no detectable amounts of diacetyl are formed.

Experimental.

Acetone.—The acetone was purified by treatment with successive small quantities of potassium permanganate until no more brown coloration appeared. It was then kept over potassium carbonate, distilled, dried over calcium chloride, and fractionated, the portion of b. p. 56·0—56·1° being collected.

Carbon Dioxide.—The gas was prepared from marble and hydrochloric acid, passed over moist copper sulphate and through sulphuric acid. Quantities of carbon dioxide were collected in a glass vessel attached to the photochemical apparatus by freezing it in a vacuum, vaporising it, and again freezing it to remove traces of oxygen and nitrogen.

Nitrogen.—The nitrogen was obtained from a cylinder and passed through alkaline pyrogallol and sulphuric acid, and sometimes over red-hot copper, before admission to the apparatus, in order to remove traces of oxygen.

Apparatus.—The photochemical set-up differed in no way from the type usually employed, except that the cylindrical photo-cell of quartz, 6·5 cm. long by 3·5 cm. internal diameter, was attached to the main vacuum line by a long quartz tube (65 cm.) terminating in a quartz-to-glass joint. This was in place of a greaseless valve, which was unprocurable. The possibility of reaction between any radicals formed and the tap grease on this joint at this distance is very remote.

A mercury vapour lamp, of the Hanovia " Homesun " type, was used as a source of ultra-violet light.

The small quantities of carbon monoxide and ethane obtained during a run were estimated with the aid of a micro-gas analysis apparatus, similar to that described by Blacet and Leighton (*Ind. Eng. Chem. Anal.*, 1933, **5**, 272). All of the gas formed during a run was pumped off by a small Toepler pump, and a portion analysed for the C_2H_6/CO ratio. This procedure is necessary to recover all of the ethane, without which the ratio obtained would not be the correct one. The ethane was determined by explosion with oxygen, the water absorbed by a phosphoric oxide bead, and the carbon dioxide by a potassium hydroxide bead. The carbon monoxide was determined by absorption in a bead of silver oxide prepared as described by Blacet and Leighton (*loc. cit.*), dried in a partial vacuum, and highly compressed. After a run, the carbon monoxide and ethane were pumped off, and the condensable material was frozen out with freezing isoamylene (— 125°) or methanol (— 90°). When carbon dioxide was present, the greater part of it was absorbed by solid potassium hydroxide, the small, residual amount being taken up by a potassium hydroxide bead during the first stage of the gas analysis. The diacetyl was estimated in separate experiments by Vizern and Guillot's method (*Ann. Falsif.*, 1932, **25**, 459), which depends on its conversion into dimethylglyoxime and comparison of the red colour then produced by nickel sulphate with that from solutions of known diacetyl content. Results were probably accurate to within 10%.

Discussion.

Some of our earlier experiments were concerned with finding out if the presence of a platinum-black-coated platinum gauze had any influence on the photodecomposition of acetone, but these were inconclusive, as the effects observed were not much outside the experimental error. When an inert gas such as nitrogen or carbon dioxide (without the gauze) was added to the acetone decomposing in light of the 2400—3130 A. region, however, very definite and reproducible results were obtained. In the experiments listed in Table I the acetone was illuminated by light of the same intensity for the same period (16 minutes) in each case. All the products of decomposition, except the carbon monoxide, were frozen out with liquid air.

The yield of carbon monoxide is increased by a factor of about 1·7. This suggests two possibilities: (1) an overall increase in the quantum yield of acetone decomposed, and (2) breakdown of the $CH_3{\cdot}CO$ radical, owing to its greater instability in the presence of gases of higher pressure. The second of these effects would manifest itself as a diminished yield of diacetyl.

Table I.

Temperature: 19—20°.

Acetone, mm. Hg.	CO_2, mm. Hg.	CO formed, c.c.	Acetone, mm. Hg.	CO_2, mm. Hg.	CO formed, c.c.
150	0	0·020	150	620	0·036
,,	,,	0·019	,,	610	0·034
,,	,,	0·020		Unilluminated	
,,	600	0·034	,,	630	0·0005

In some fresh experiments diacetyl was tested for, not only in the condensate frozen out with liquid air after each run, but also in the reaction vessel itself (Table II).

TABLE II.

Temperature: 18—20°.

Added gas.	Pressure of added gas, mm.	Pressure of acetone, mm.	Diacetyl formed, mg.	Added gas.	Pressure of added gas, mm.	Pressure of acetone, mm.	Diacetyl formed, mg.
—	—	150	2·0	CO_2	590	150	0
—	—	155	2·2	N_2	600	150	0
—	—	140	2·0	,,	640	140	0
CO_2	620	150	0	,,	640	150	0

If diacetyl is not formed under these conditions, or only formed in minute, undetectable amounts, the only analysable products of the photoreaction other than some polymerised material (which, however, is considered to arise from the diacetyl) will be carbon monoxide and ethane, the latter being formed from the union of two methyl radicals. (A small amount of methane is sometimes found, even at room temperature, owing to secondary reactions, such as $CH_3 + CH_3{\cdot}CO{\cdot}CH_3 = CH_4 + CH_2{\cdot}CO{\cdot}CH_3$.) The ratio C_2H_6/CO in the absence of diacetyl should be unity (see p. 589). The results of our micro-analyses confirm this (Table III), although it must be admitted that with the " mixed light " (2400—3130 A.) of high intensity the ratio C_2H_6/CO is not very high (1·25—1·40) in the absence of the inert gas.

TABLE III.

Temp.	22°	22°	21°	21°	22°	19°	24°	24°	18°	20°	21°	18°
Press. of acetone (mm.)	149	149	154	154	150	163	175	175	158	162	168	148
Press. of CO_2 (mm.) ...	0	0	0	0	0	0	540	540	620	590	580	610
C_2H_6/CO	1·25	1·34	1·25	1·35	1·40	1·32	0·88	0·92	0·98	1·13	1·09	0·94

Our explosion results, obtained with oxygen and the gas left after the absorption of the carbon monoxide, indicated that a small amount of methane may have been formed during the photolysis, but this in no way affects our general conclusions.

There are two ways in which the inert gas may act to prevent the formation of diacetyl: (1) by increasing the collision frequency of the acetyl radical with other molecules, thereby enabling it to acquire enough activation energy to dissociate into methyl and carbon monoxide. Gorin (*J. Chem. Physics*, 1939, **7**, 256) estimates that the energy required for this process is 17,000 cals. [in Spence and Wild's scheme for the photodissociation of acetone (1941, *loc. cit.*), the stability of $CH_3{\cdot}CO$ is shown to be pressure-dependent in the equation $CH_3{\cdot}CO + M = CH_3 + CO + M$]; (2) by hindering the diffusion of acetyl radicals to the walls of the reaction vessel, where they combine to give diacetyl: $2CH_3{\cdot}CO = CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3$.

The increase in the quantum yield of carbon monoxide must be linked with this diacetyl factor, but it need not be attributed solely to this, and indeed, the presence of the inert gas may act adversely in preventing the breakdown of the excited acetone molecules found in the banded region, by assisting in their deactivation. The increase in the carbon monoxide yield may therefore be actually less than the expected amount due to this deactivation. The quantum yield for acetone decomposed will of course be increased, because destruction of the acetyl radical inhibits the back reaction $CH_3{\cdot}CO + CH_3 = CH_3{\cdot}CO{\cdot}CH_3$.

Let a and b be the concentrations of ethane and carbon monoxide, respectively, found in absence of inert gas, and x = increased concentration of the monoxide in presence of inert gas. Then, using our mean results for C_2H_6/CO ratios, we have: $a/b = 1{\cdot}32$, $(a + 0{\cdot}5x)/(b + x) = 1{\cdot}0$, whence $(b + x)/b = 1{\cdot}64$. Our experimental factor 1·7 expressing the increased yield of carbon monoxide is very close to this value, but more accurate experiments will be necessary to show whether or not the deactivation of excited acetone molecules by the inert gas has any considerable influence on the yield of carbon monoxide. Experiments were begun with only continuum light (~2537 A.), but have had to be interrupted.

Our results are to some extent comparable with those of Howe and Noyes (*loc. cit.*), who used inert gases in the 1800—1900 A. region. They found that the gases increased the quantum yield for acetone decomposed, but they were not concerned with the formation of diacetyl, and assumed that the inert gas assisted in breaking up the excited acetone molecules.

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160. *The Magnetic Susceptibility of Certain Organic Compounds. Part I. The Constitution of the* p*-Benzoquinone, Quinol, and Quinhydrone System.*

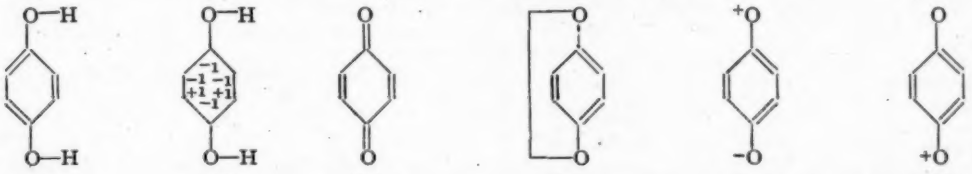
By HABIB MIKHAIL and FAWZY GHALI BADDAR.

Magnetic susceptibility measurements carried out on quinhydrone and its constituents showed that the law of additivity holds. Three resonance formulæ are suggested for quinone.

MANY investigators (cf. Table II) have measured the magnetic susceptibility of quinone, quinol, and quinhydrone with a view to elucidate the type of linkage between the components of the quinhydrone molecule,

but none of these authors has discussed the constitution of the components in the light of their magnetic susceptibility values. The object of the present investigation was to determine these values and apply the results to the elucidation of the structures.

Gray and Cruickshank's method (*Trans. Faraday Soc.*, **1935**, **31**, 1491) was adopted for calculating the theoretical values. The experimental values obtained for quinol (cf. Table II) are in good agreement with the calculated values based on Gray and Cruickshank's suggestion (*loc. cit.*) that the benzene nucleus oscillates in equal times between the Kekulé and the internal-ionic form, (I) and (II).



(I.) (II.) (III.) (IV. (V. (VI.)

Table I shows the method of calculation for formula (III) for benzoquinone, that for (IV) and (V) being similar. In (IV), the bond depression for O—O was obtained by analogy from N→O. As (IV) and (V) gave $\chi \times 10^5 = 40{\cdot}746$ and $43{\cdot}740$, respectively, the mean is **39·282**.

TABLE I.

No. of atoms.	Charge on each.	Diamagnetism of each.	Total diamag.	Bond depression.
4C	−0·04	C^{-1} 0·04 × 14·69 = 0·587		2C=C = 19·0
		C^{0} 0·96 × 9·96 = 9·562	40·597	2C=O = 20·56
2C	+0·42	C^{+1} 0·42 × 6·64 = 2·789		4C—C = 7·92
		C^{0} 0·58 × 9·96 = 5·777	17·132	4C—H = 2·12
4H	+0·04	H^{+1} 0·04 × 0·0		
		H^{0} 0·96 × 2·372 = 2·278	9·112	Total 49·60
2O	−0·42	O^{-1} 0·42 × 9·40 = 3·948		
		O^{0} 0·58 × 7·09 = 4·112	16·120	
		Total	82·961	
		Bond depression	49·600	
		Mol. diamagnetism	33·361	

Several experimental values have been reported for *p*-benzoquinone (see Table II); Lonsdale (*Proc. Roy. Soc.*, 1937, **159**, 153) concluded from magnetic data that the double bonds in the nucleus are indicated by a small anisotropy, and stated that the evidence is definitely against the fixation of the double bonds, at least when the molecule is in a strong magnetic field. Although Palacios and Foz's value (*Anal. Soc. Fis. Quim.*, 1935, **33**, 627) satisfies the simple formula for benzoquinone (III), based on Gray and Cruickshank's method, yet it is lower than that found by other authors. Similar anomalous electric dipole moments in solution were observed by Jenkins *et al.* (*Nature*, 1935, **136**, 990) and were attributed either to a general solvent effect or to an abnormally large atomic polarisation. Coop and Sutton (J., 1938, 1277) measured the dipole moment of *p*-benzoquinone in the vapour state and concluded that their result was in good agreement with a simple quinone structure (III) in resonance with others of the Kekulé type, (IV) (Pauling and Sherman), (V), and (VI) (Robinson). Our high value is in harmony with the suggestion that the molecule resonates in equal times between structures (III), (IV), and (V).

For quinhydrone several structures based on chemical evidence have been put forward (cf. Pfeiffer, "Organische Molekülverbindungen," 1927). Our experimental values differ slightly from those of Banerjee (*Z. Krist.*, 1938, **100**, 316), but both values indicate that the law of additivity holds well within the range of experimental errors. The bond linking the quinol and the quinone molecule could not be represented other than by the conventional dotted line.

Calculations.—Calculations of magnetic susceptibility values based on Gray and Cruickshank's method give the following results.

For quinol the values obtained for the resonance forms (I) and (II) are 46·513 and 82·595 respectively; the mean is **64·554**, in good agreement with our experimental value (cf. Table II).

EXPERIMENTAL.

Gouy's method was used, since Banerjee's (*loc. cit.*) could not be applied to all our compounds. The field strength was of the order of 13,000 gauss produced by a Weiss electromagnet. The container was a stoppered Monax glass tube, 0·6 cm. in diameter and 16 cm. long. The gap between the pole-pieces of the electromagnet was 1·1 cm. The pole-faces were 1·5 cm. in diameter, with an angle of 39° for producing maximum homogeneity. The usual precautions were adopted.

Hoare's formula (*Proc. Roy. Soc.*, 1934, **147**, 88) was used for calculation. The meniscus correction was eliminated by locating the lower flat edge of the tube exactly centrally between the pole-pieces of the electromagnet.

Materials.—The solvents were purified according to Weissberger and Proskauer ("Organic Solvents," 1935). Quinol, repeatedly crystallised from purified benzene, had m. p. 170·3°. *p*-Benzoquinone was freed from quinhydrone by steam

distillation in presence of ferric chloride under reduced pressure at 60°; after extraction by ether and two crystallisations from light petroleum, it had m. p. 115·8° (cf. Zimmerli and Lyon, U.S.P., 1,883,284, 1933). Quinhydrone, prepared from its constituents, had m. p. 171°.

In order to secure uniformity of packing, the substance was finely powdered in an agate mortar, and introduced into the specimen tube in small amounts, being packed after each addition by gentle tapping, followed by pressing down with a flat-ended glass rod just sliding into the tube. Consistency of results after different packings is regarded as proof of random orientation.

Results.—Typical results for $\chi \times 10^6$ are given in Table II.

TABLE II.

	Experimental values.					Calculated values.	
Substance.	(i).	(ii).	(iii).	(iv).	(v).	Pascal.	Gray and Cruickshank.
Benzoquinone	38·20	33·31	41·28	40·0	40·0 [a]	40·80	39·28
Quinol	64·73	64·58	—	—	64·0 [a]	66·82	64·55
Quinhydrone	105·0	84·23	—	—	111·7 [b]	107·62	103·84

(i) Authors' values. (ii) Palacios and Foz's values (*loc. cit.*). (iii) Pascal's value on powder (*Bull. Soc. chim.*, 1911, **9**, 177, 809). (iv) Lonsdale's mean value on a crystal (*loc. cit.*). (v, *a*) Krishnan and Banerjee's mean values on crystals (*Phil. Trans.*, 1935, *A*, **234**, 265). (v, *b*) Banerjee's mean value on a crystal (*loc. cit.*).

We thank Prof. Frank L. Warren for suggesting this research.

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161. *Experiments on the Synthesis of Purine Nucleosides. Part VIII. The Determination of the Lactol Ring Structures of Purine Glycosides by Periodate Oxidation.*

By B. LYTHGOE and A. R. TODD.

Periodate oxidation of purine glycosides in which the sugar residue is attached to one of the imidazole nitrogen atoms is shown to follow a course identical with that demonstrated for the simple *O*-glycosides by Jackson and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 994). Application of the method permits a convenient determination of the structure of the lactol ring in such *N*-glycosides. The 9-*d*-xylosido-2-methyladenine described in Part VI (this vol., p. 318) is shown to be a pyranoside. Some further possible applications of the method to the determination of structure in the nucleoside and nucleotide fields are considered.

THE experiments herein reported had as their object the development of a method for determining whether the 9-glycosidopurine derivatives obtained by application of our general synthetic method (cf. Part VI, *loc. cit.*) were furanosides or pyranosides, a question of considerable importance in view of our intention to apply similar methods of synthesis to the production of adenosine (9-*d*-ribofuranosidoadenine). Ring structures of *N*-glycosides are known with certainty in relatively few cases. Kuhn and Ströbele (*Ber.*, 1937, **70**, 773), relying on tritylation evidence, ascribed a furanoside structure to the *o*-nitroaniline pentosides obtained by their glycosidisation method; as is already known (cf. Watters, Hockett, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1528), proof obtained in this way is by no means rigorous. Application of the classical methylation method has demonstrated rigidly the pyranoside nature of *d*-glucose-*p*-toluidide (Kuhn and Dansi, *Ber.*, 1936, **69**, 1745) and the furanoside nature of adenosine, guanosine, and uridine (Levene and Tipson, *J. Biol. Chem.*, 1932, **94**, 809; **97**, 491; 1933, **101**, 529). This method, satisfactory in most cases, requires the use of relatively large amounts of material, whereas for our purposes a method conveniently applicable on the decigram scale seemed desirable.

In the *O*-glycoside series such a method is available in the periodate oxidation procedure developed by Jackson and Hudson (*loc. cit.*); titrimetric investigation of the reaction (cf. Hudson *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 1530; 1943, **65**, 64), possible once the course of the oxidation is established, gives a method for the semi-micro-determination of ring structure in this series. It seemed possible that this method might be capable of extension to purine glycosides in which the sugar residue is attached to one of the imidazole nitrogen atoms, and experiments were undertaken to decide whether the periodate oxidation of such compounds does, in fact, follow the same course.

Suitable models for our purpose, containing a furanoside structure, were found in adenosine, guanosine, muscle adenylic acid (adenosine-5′-phosphate), and yeast adenylic acid (adenosine-3′-phosphate). As pyranoside models we selected the readily accessible theophylline hexosides and pentosides produced by reaction of theophylline silver with the appropriate pyranose acetohalogen sugar (Fischer and Helferich, *Ber.*, 1914, **47**, 217). These pyranosides, in which the sugar is attached to N_7 in the imidazole ring (Gulland, Holiday, and Macrae, J., 1934, 1639), are of suitable stability to hydrolytic agents (comparable with that of the naturally occurring purine nucleosides); moreover, the ring structure of the sugar residue is known from the mode of formation, and has been verified in the case of theophylline-7-*l*-arabinoside by the unambiguous methylation procedure (Pryde and Williams, J., 1933, 640).

The amount of sodium metaperiodate required for the oxidation of the glycosides investigated, together with the amounts of formic acid liberated in the reaction (both determined titrimetrically), and the termina

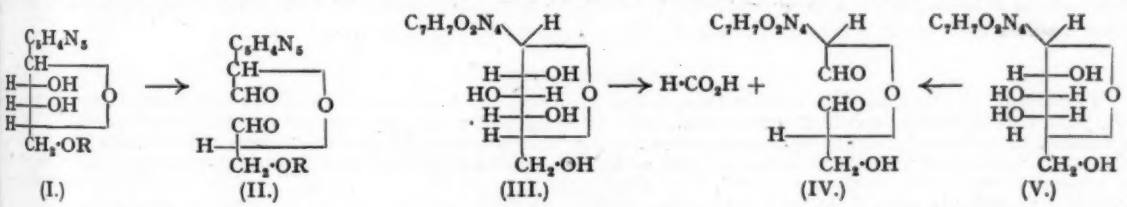
rotations of the reaction solutions are set out in the table. It was previously verified that the parent bases, theophylline, adenine and guanine, do not react with sodium metaperiodate under the conditions employed for oxidation of the glycosides, and that the latter (and hence presumably their scission products) are not sufficiently dissociated to interfere seriously with the estimation of any formic acid liberated in the reaction.

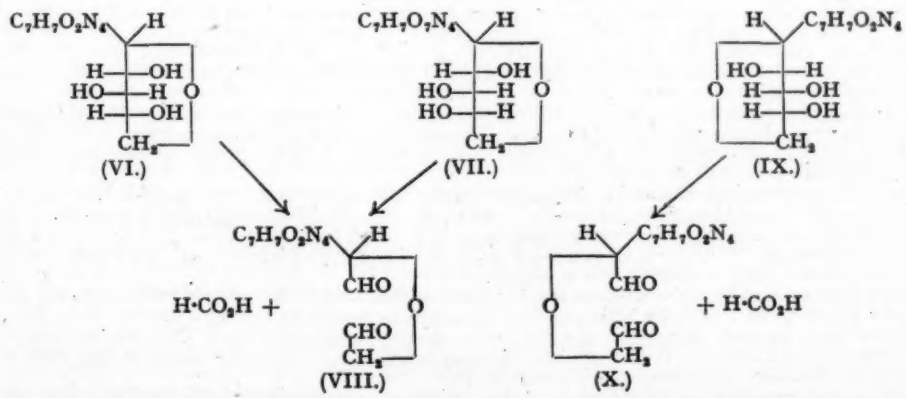
Glycoside.	Reference.	Amount of glycoside (millimols.).	$NaIO_4$ uptake (mols. per mol. of glycoside).	$H{\cdot}CO_2H$ formed (mols. per mol. of glycoside).	Rotation of product * ($[M]_D^{18°} \times 10^{-4}$).
Theophylline-7-(β)-*d*-gluco-pyranoside (III)	Fischer and Helferich, *loc. cit.*	0·4505	2·01	0·985	−1·29°
Theophylline-7-(β)-*d*-galacto-pyranoside (V)	Helferich and Kühlewein, *Ber.*, 1920, **53**, 17.	0·347	2·07	0·955	−1·28
Theophylline-7-(β)-*d*-xylo-pyranoside (VI)	Levene and Sobotka, *J. Biol. Chem.*, 1925, **65**, 463.	0·445	2·02	0·965	+1·47
Theophylline-7-(α)-*d*-arabo-pyranoside (VII)	Present paper.	0·400	1·98	0·98	−1·49
Theophylline-7-(α)-*l*-arabo-pyranoside (IX)	Helferich and Kühlewein, *loc. cit.*	0·445	2·01	0·98	+1·48
Adenosine (I, R = H)	Levene and Tipson, *J. Biol. Chem.*, 1932, **94**, 809.	0·595	1·04	0	—
Guanosine	*Idem, ibid.*, 1932, **97**, 491.	0·6325	1·00	0	—
Muscle adenylic acid (I, R = PO_3H_2)	Levene and Stiller, *ibid.*, 1934, **104**, 299.	0·157	1·01	—	—
Yeast adenylic acid	Levene and Harris, *ibid.*, 1932, **98**, 9; 1933, **101**, 419.	0·169	0	—	—
9-*d*-Xylosido-2-methyl-adenine	Baddiley, Lythgoe, and Todd, this vol., p. 318.	0·318	2·00	0·865	—

* Rotations determined separately on larger samples.

These results are parallel to those obtained with the simpler *O*-glycosides, pyranosides requiring 2 mols. of metaperiodate and liberating 1 mol. of formic acid, whilst furanosides require only 1 mol. of metaperiodate, oxidation taking place without production of formic acid. In the furanosides, the point of attack (C_2–$C_{3'}$) of the oxidising agent is shown clearly by the above results, muscle adenylic acid (I, R = PO_3H_2) like adenosine (I, R = H) consuming 1 mol. of the oxidant, whereas yeast adenylic acid, where the hydroxyl at $C_{3'}$ is protected by a phosphoryl residue, fails to react.

Further evidence of the identity of the course of oxidation with that in the *O*-glycoside series is given by the nature of the scission products formed in the reaction. From oxidation of theophylline-7-(β)-*d*-glucoside (III) a crystalline substance was isolated in good yield, giving the reactions of an aldehyde and having the composition required by a monohydrate of the *dialdehyde* (IV). Although complete degradative proof of





structure was not obtained, theophylline was isolated in good yield from the products of acid hydrolysis of the compound, and there can be little doubt of the correctness of the constitution assigned, since, as anticipated from the identity of configuration at C_1, and $C_{2'}$ in (III) and (V), the same compound was obtained by periodate

oxidation of theophylline-7-(β)-*d*-galactoside (V). Oxidation of the pentopyranosides must also follow the expected course, since the same scission product (VIII) is produced from both theophylline-7-(β)-*d*-xyloside (VI) and theophylline-7-(α)-*l*-arabinoside (VII), while the enantiomorphous dialdehyde (X) arises from scission of theophylline-7-(α)-*d*-arabinoside (IX). The dialdehydes (VIII) and (X) could not be isolated crystalline owing to their inconvenient solubilities, and were identified by measurement of optical rotation. The designation of the *d*-glucoside, *d*-galactoside, and *d*-xyloside of theophylline as β-glycosides and of the *d*- and *l*-arabinosides as α-glycosides involves the assumption that, as is usual in such reactions, Walden inversion takes place when the halogen of the acetohalogen sugar is exchanged for the theophylline residue. Although a high degree of probability attaches to this assumption, we are aware that it cannot be regarded as rigorously proved, and it may be pointed out that the validity of those conclusions drawn above which depend on assumption of the configurations at C_1, in the theophylline glycosides, is unaffected whether the formation of the latter involves Walden inversion or not, since the mechanism is almost certainly the same in each case.

Having established the course of the oxidation, we could now proceed with the investigation of the ring structure of the synthetic 9-*d*-xylosido-2-methyladenine described in Part VI (*loc. cit.*). As shown in the table, this glycoside was found to consume 2 mols. of sodium metaperiodate and to liberate an amount of formic acid approaching 1 mol.; it is therefore a pyranoside and should be designated as a 9-*d*-xylopyranosido-2-methyladenine; presumably all the other purine and pyrimidine xylosides described in Part VI are also pyranosides.

The procedure here described is not directly applicable in its present form to determination of ring structure of 4-glycosidaminopyrimidine derivatives or of 6-glycosidaminopurine derivatives. The amounts of metaperiodate consumed by, and of formic acid liberated from, these compounds indicate a more extensive breakdown of the sugar residue. A possible explanation is that oxidative scission of the C_1–C_2 linkage takes place in these cases. Periodate fission of *N*-monosubstituted 1 : 2-amino-alcohol systems is known to occur (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1939, **61**, 1614; see also Neuberger, J., 1941, 47), although Carter, Glick, Norris, and Philips (*J. Biol Chem.*, 1942, **142**, 449) claim that *N*-benzoylation of sphingosine protects it against attack by periodic acid. Closer examination of the behaviour of our glycosidamino-compounds with sodium metaperiodate is in progress and will be described in a subsequent communication.

Some further important aspects of the periodate oxidation method may be pointed out. It appears to afford an attractive method of settling the ring structure of the sugar residue in other purine ribosides (*e.g.*, uric acid riboside, crotonoside) and in the pyrimidine and purine deoxyribosides from thymus nucleic acid. It should also be capable of affording evidence concerning the location of the phosphoryl residues in the adenosine polyphosphoric derivatives, and of giving information concerning the structures of the more complex breakdown products of ribonucleic acids. Finally, by application of this method approach to the problem of the configuration of the glycosidic linkage in the natural nucleosides should be possible, since periodate degradation of Hilbert and Johnson's 3-*d*-glucosidouracil (*J. Amer. Chem. Soc.*, 1930, **52**, 4489) and of Fischer and Helferich's 9-*d*-glucosidoadenine (*loc. cit.*; Gulland and Story, J., 1938, 259) should give compounds identical or stereoisomeric with those from natural uridine and adenosine respectively, and the β-configuration in the synthetic compounds is known with a high degree of probability from their mode of formation. Investigations along these various lines are in active progress and will be reported in due course.

Experimental.

Preparation of Materials.—Acetylated theophylline glycosides were prepared by Gulland and Macrae's modification (J., 1933, 662) of Fischer and Helferich's original procedure (*loc. cit.*); except in the preparation of tetra-acetyl-7-(β)-*d*-glucoside, the acetochloro-sugar was used instead of the acetobromo-sugar in the reaction with theophylline silver. Triacetyl theophylline-7-(β)-*d*-xyloside, described by Levene and Sobotka as an amorphous powder, $[\alpha]_D$ −21·9° (*c*, 4·25 in methyl alcohol), was obtained as plates from ethyl alcohol, m. p. 147—148°, $[\alpha]_D^{18\cdot5°}$ − 23·9° (*c*, 3·3 in chloroform) (Found: C, 49·5; H, 5·0. Calc. for $C_{18}H_{22}O_9N_4$: C, 49·3; H, 5·0%).

Triacetyl theophylline-7-(α)-*d*-arabinoside formed plates from ethyl alcohol; m. p. 215—216°, $[\alpha]_D^{18°}$ −36·7° (*c*, 3·0 in chloroform). Pryde and Williams (*loc. cit.*) give $[\alpha]_{5461}^{21°}$ +42·1° (*c*, 0·605 in chloroform) for the enantiomorph; our own preparation of the enantiomorph had m. p. 215—216°, $[\alpha]_D^{18°}$ +36·6° (*c*, 3·0 in chloroform); triacetyl theophylline-7-(α)-*dl*-arabinoside separated from an equimolecular solution of the enantiomorphs in ethyl alcohol, m. p. 233—234°, $[\alpha]_D^{18°}$ ±0° (*c*, 3·92 in chloroform).

Theophylline glycosides, obtained by deacetylation of the acetates in the usual manner, were dried to constant weight at 140° in a vacuum over phosphoric oxide before use. Theophylline-7-(β)-*d*-xyloside, needles (hydrated) from water, m. p. 249—251° (decomp.); the anhydrous material had $[\alpha]_D^{18°}$ −35·5° (*c*, 1·78 in water); Levene and Sobotka (*loc. cit.*) give m. p. 229°, $[\alpha]_D$ −27·4° (*c*, 3·61 in water).

Theophylline-7-(β)-d-*arabinoside* separated as needles (hydrated) from water, m. p. 264—267°; the anhydrous material had $[\alpha]_D^{18°}$ −36·3° (*c*, 2·15 in water) (Found: C, 46·1; H, 5·1; N, 17·9. $C_{13}H_{16}O_6N_4$ requires C, 46·1; H, 5·1; N, 17·9%). Our preparation of the enantiomorph had m. p. 272—274°, $[\alpha]_D^{18°}$ +36·3° (*c*, 2·04 in water); for the latter, Helferich and Kühlewein (*loc. cit.*) record m. p. 276—277°, $[\alpha]_D^{18°}$ +33·87° (*c*, 2·5 in water), and Pryde and Williams (*loc. cit.*) give m. p. 282—284°, $[\alpha]_{5461}^{17°}$ +39·9° (*c*, 2·5 in water).

Adenosine and guanosine were prepared from B.D.H. yeast nucleic acid by hydrolysis with aqueous pyridine (Bredereck, Martini, and Richter, *Ber.*, 1941, **74**, 694) and dried to constant weight at 110° in a vacuum over phosphoric oxide before use. Muscle adenylic acid, for the gift of which we are deeply indebted to Dr. F. Dickens, was a sample obtained from Messrs. Fraenkel and Landau. It was similarly treated before use. The yeast adenylic acid used was a sample obtained through the courtesy of Messrs. Roche Products Ltd.

Fission of Glycosides with Sodium Metaperiodate.—(a) *Titrimetric investigation.* The glycoside (0·1—0·7 millimol.) was dissolved in a convenient volume of hot water in a graduated flask, the solution cooled rapidly to 25°, treated with 0·2655M-sodium metaperiodate (5 c.c.), diluted with water to a known volume, and set aside at 19°. After a suitable interval an aliquot was removed, and the unchanged metaperiodate estimated iodometrically by the method of Barneby (*J. Amer. Chem. Soc.*, 1916, **38**, 330), using 0·1N-sodium arsenite; this process was repeated till no further uptake of

metaperiodate took place. Formic acid was then estimated in an aliquot by dilution with water and titration to the methyl-red end-point with 0·01N-sodium hydroxide (cf. Jackson and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1530). Experience of the effect of concentrations of reactants and of the nature of the glycoside used enabled the time required for completion of the reaction to be gauged, and so decreased the number of titrations required; *e.g.*, oxidation of guanosine (179 mg. in 250 c.c. of water) was complete after 26 hours; oxidation of 9-*d*-xylosido-2-methyladenine (89·3 mg. in 250 c.c. of water) took 60—70 hours for completion. Titration of muscle and yeast adenylic acids was carried out in the same manner, 1 equiv. of sodium hydroxide being used to effect dissolution in the first place.

(b) *Polarimetric investigation.* Theophylline pentosides (*ca.* 500 mg.) were dissolved in water (25 c.c.) containing an excess (*ca.* 10%) of sodium metaperiodate, and the rotation of the solution was followed ($l = 2$) till constancy was attained. Investigation of the theophylline hexosides was carried out in the same way, but the initial concentration of glycoside could not conveniently be increased beyond 4 mg./c.c. owing to a tendency of the scission product to separate from solution; on this account the use of a 4-dm. tube for measurement of rotations was found necessary.

Isolation of α-(Theophylline-7)-α′-hydroxymethyldiglycollic Aldehyde.—(a) *From theophylline-7-(β)-d-glucopyranoside.* The glucoside (1 g.) in water (15 c.c.) was allowed to stand with addition of 0·2655M-sodium metaperiodate (13 c.c.) at 15° for 60 hours, and the monohydrate of the *dialdehyde* collected and recrystallised from water. It separated as dense crystalline aggregates from concentrated solutions, or as needles from dilute solutions; yield, 0·8 g. On rapid heating, it melted with evolution of water vapour at 177—179°; on slow heating, sintering took place at 177—179°; m. p. 207—208° (decomp.); $[\alpha]_D^{19°}$ −42° ($c = 0·25$ in water) (Found: C, 43·4; H, 4·9; N, 17·0. $C_{13}H_{14}O_6N_4.H_2O$ requires C, 43·9; H, 4·9; N, 17·1%). Attempts to dehydrate the substance at 160° in a high vacuum over phosphoric oxide were unsuccessful. Schiff's test was positive. Aqueous solutions gave with phenylhydrazine acetate a white precipitate, recrystallisation of which could not be effected. An attempt to convert the substance into a crystalline strontium salt of the corresponding dicarboxylic acid by oxidation with bromine in presence of strontium carbonate was unsuccessful.

Estimation of aldehyde groups. The above monohydrate (63·6 mg.; 0·194 millimol.), treated with potassium hydrogen sulphite according to Ripper's method (*Monatsh.*, 1900, **21**, 1079), combined with 0·390 millimol. of the hydrogen sulphite (Calc. for 2CHO groups: 0·388 millimol.).

Hydrolysis. The dialdehyde monohydrate (200 mg.) was refluxed for 1½ hours with 10% hydrochloric acid (10 c.c.), the solution evaporated under reduced pressure at 40°, and the residue dissolved in water and again evaporated. Crystallisation from water (3 c.c.) gave theophylline as needles, m. p. 266·5—267·5°, undepressed on admixture with an authentic specimen of theophylline, m. p. 267—268°; yield, 75 mg.

(b) *From theophylline-7-(β)-d-galactopyranoside.* The galactoside (650 mg.) in water (15 c.c.) was set aside at 18° with addition of 0·2640M-sodium metaperiodate (16 c.c.). The dialdehyde monohydrate (450 mg.), collected after 60 hours, separated from water in the same crystalline form as the material obtained by route (a) above, and alone and in admixture with this material showed the same behaviour on heating; m. p. 207—208°, $[\alpha]_D^{19°}$ −41° (*c*, 0·25 in water) (Found: C, 44·1; H, 5·2%).

Attempts were made to isolate the product from sodium metaperiodate fission of theophylline-7-(α)-*l*-arabopyranoside. Periodate and iodate were removed from the reaction solution by addition of barium chloride, and excess of barium removed as barium sulphate by addition of sodium sulphate solution. The residue from evaporation of the solution was extracted with warm alcohol, evaporation of which left the fission product as a gum, very soluble in water and alcohol. Crystallisation of this material could not be effected.

Grants and gifts of material from Imperial Chemical Industries Limited and Roche Products Limited are gratefully acknowledged.

THE UNIVERSITY, MANCHESTER. [*Received, August 8th*, 1944.]

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162. *The Infra-red Spectrum of Phenylacetylene.*

By H. W. THOMPSON and P. TORKINGTON.

The infra-red absorption spectrum of phenylacetylene has been measured between 3 and 20 μ. The results have been correlated with data from the Raman spectrum, and a consideration of several related molecules suggests a series of magnitudes for some of the vibrations of the phenyl nuclear skeleton.

THE Raman spectra of several substituted acetylenes including phenylacetylene have been measured by Murray and Cleveland (*J. Amer. Chem. Soc.*, 1938, **60**, 2664; 1940, **62**, 3185; *J. Chem. Physics*, 1940, **8**, 133), who have also measured the infra-red absorption spectrum of phenylmethylacetylene and compared the observed absorption frequencies with the Raman intervals. We have recently measured the infra-red spectrum of phenylacetylene, which can now be correlated with the Raman spectrum. With molecules of this degree of complexity there are so many fundamental vibration frequencies that a satisfactory normal co-ordinate treatment is at present impracticable, and attempts to correlate the frequencies with motions of particular parts of the nuclear skeleton must in the first instance be based upon correlation of the data with a series of closely related molecules.

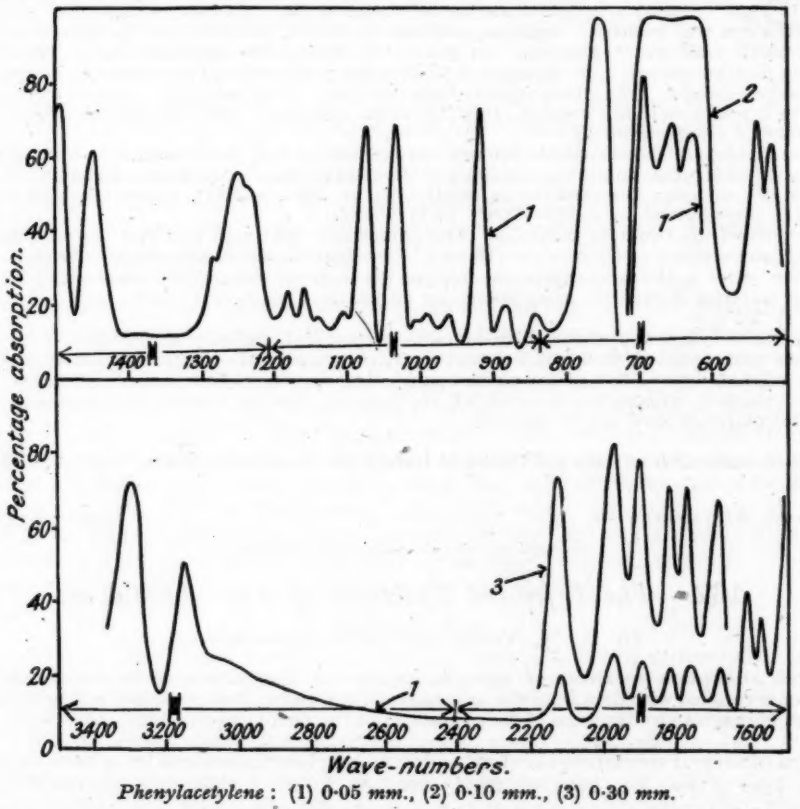
The phenylacetylene was a synthetic product, kindly supplied by the Research Department of I.C.I. Ltd. (Dyestuffs Division). It was distilled before use; b. p. 142°. The liquid was studied in absorption cells about 0·05, 0·1, and 0·3 mm. thick, made by separating a pair of polished rock-salt or sylvine plates with a metal washer. A few measurements on some of the strongest bands were also made with the vapour, low pressures being used in a cell 20 cm. long. The spectrometers used have already been described by us (*Proc. Roy. Soc.*, in the press).

Results and Discussion.—The absorption curves for the range 500—3300 cm.$^{-1}$ (20—3 μ) are shown in the figure, and Table I lists the positions of the bands (in wave-numbers), together with the frequencies obtained from the Raman spectrum by Murray and Cleveland. There is a marked correspondence between the infra-red and the Raman data, similar to that found for phenylmethylacetylene. As might have been expected, the frequencies which are most strongly absorbed in the infra-red tend to be relatively weak in the Raman effect, and *vice versa*.

TABLE I.

Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
	164(6)	758 s	760(5)	1074 s		1282 w	1281(1)	1770 w	
	353(4)	842 w		1103 w			1337(1)	1820 w	
	465(3)	883 w		1140 w			?1380(1)	1900 w	
518 m	517(2)	915 s		1156 w	1155(2)	1450 s	1447(1)	1972 w	
535 m	530(3)	956 w		1180 w	1176(4)	1493 s	1489(2b)	2128 w	2113(10)
625 m	621(4b)	990 w			1196(6)	1582 w			3066(8)
655 m		1002 w	1001(7)	1230 m	1230(1)	1608 m	1601(9)	3155 m	3142(1)
693 s		1030 s	1027(2)	1250 m		1685 w		~3300 s	3288(3)

Now with both phenylacetylene and phenylmethylacetylene there will be a set of frequencies above about 1400 cm.$^{-1}$ which are determined essentially by vibrations of C–H bonds and the C≡C link. Thus the valency vibrations of C–H bonds will lie around 3000 cm.$^{-1}$, and that of the C≡C bond at about 2200, while C–H deformations will give rise to frequencies in the region of 1400 cm.$^{-1}$. The other normal modes, which will nearly all



Phenylacetylene : (1) 0·05 *mm.*, (2) 0·10 *mm.*, (3) 0·30 *mm.*

involve motions within the phenyl nucleus, will have values below about 1400 cm.$^{-1}$. We may therefore compare the values found in this range for phenylacetylene with those of phenylmethylacetylene. The five most intense infra-red bands of the former lie at 693, 758, 915, 1030, and 1074 cm.$^{-1}$. There is a striking parallelism with the most intense bands of the latter, which lie at 702, 754, 909, 1024, and 1064, cm.$^{-1}$, although another strong band is found at 526 cm.$^{-1}$. The last band might be correlated with one or other of the bands found with phenylacetylene at 518 and 535 cm.$^{-1}$, but this is less certain. We might therefore infer that the five principal bands just referred to are associated with vibrations of the phenyl nucleus.

As a further test of this, comparison can now be made with the spectra of other related molecules. Thus, the most intense bands in the spectrum of styrene below 1400 cm.$^{-1}$ (Thompson and Torkington, *Proc. Roy. Soc.*, in the press) lie at 700, 775, 911, 993, 1025, and 1083 cm.$^{-1}$. It was shown previously that two of these, *viz.*, 911 and 993 cm.$^{-1}$, are definitely associated with motions of the vinyl part of the nuclear skeleton. On the other hand, the band at 911 cm.$^{-1}$ is abnormally broad, and may well comprise a close pair at, say, 905/910 cm.$^{-1}$. This would leave as the unexplained strong bands 700, 775, 905, 1025, and 1083 cm.$^{-1}$, which correspond excellently with the five magnitudes found for the phenylacetylenes.

The correlation can be examined further by reference to the infra-red spectra of benzene and alkylbenzenes. These spectra and their correlation will be published elsewhere (Sutherland, Thompson, Turner, and others), but we may note that the main infra-red bands below 1400 cm.$^{-1}$ occur at the following frequencies :

Toluene	730	895	1035	1078	Propylbenzene	740	905	1030	1090
Ethylbenzene	745	905	1035	1090	*iso*Propylbenzene ...	762	905	1030	1082

With the propylbenzenes there are several other strong bands which appear to be more closely connected with oscillations in the side chain. We may also note that benzene has its most intense bands at 670 and 1035 cm.$^{-1}$.

All this evidence supports the argument that the following frequencies (cm.$^{-1}$) are associated with motions within the phenyl nucleus :

Phenylacetylene	758	915	1030	1074
Phenylmethylacetylene	754	909	1024	1064

It is possible that the frequencies 693 of phenyl- and 702 of phenylmethyl-acetylene relate to deformations involving the side-chain skeleton. On the other hand, if this were so, we might expect the analogue with styrene to be markedly affected by the change from triple to double carbon–carbon bond, whereas it lies at 700.

A more detailed discussion of these correlations will be deferred until data on related molecules are available, and the spectra of some of the saturated aromatic hydrocarbons have been measured between 14 and 20 μ.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, May 25th*, 1944.]

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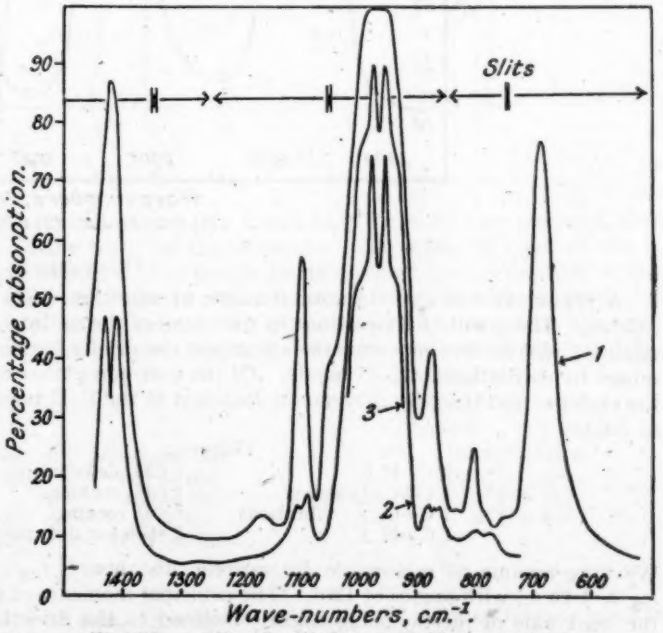
163. *The Vibrational Spectra of Acrylonitrile and Perbunan.*

By H. W. THOMPSON and P. TORKINGTON.

The spectrum of acrylonitrile has been measured over a wide range in the infra-red. A consideration of the results together with Raman data suggests a probable assignment of magnitudes to the normal vibrational modes. The spectrum of a sample of perbunan has also been measured and some suggestions have been made about the structure of this molecule.

A SURVEY has recently been made of the infra-red absorption spectra of a large number of polymeric substances and of their associated monomers and related simple molecules (Thompson and Torkington, *Proc. Roy. Soc.*, in the press). One of the main objects of this work was to decide between different possible molecular structures and to determine the course of several polymeric reactions. In the course of the work the vibrational spectrum of acrylonitrile was measured, not only because of its relationship with the vinyl halides but also since it is a component in the co-polymerisation with butadiene to form the " perbunan " class of synthetic rubber. The moments of inertia of acrylonitrile are fairly small, and it was possible to resolve the rotational contour of some of the absorption bands of the vapour. The use of this band contour and other considerations has made a vibrational analysis possible, leading to a satisfactory assignment of magnitudes to the normal vibration frequencies of the molecule. Some preliminary comments can also be made about the nature of the sample of perbunan studied.

FIG. 1.



(1) 0·08 *mm. liquid*; (2) 7-*cm. cell*, 80 *mm. vapour*; (3) 7-*cm. cell*, 40 *mm. vapour*.

EXPERIMENTAL.

The acrylonitrile was a sample supplied by I.C.I. Ltd., Dyestuffs Division, stabilised over copper powder. It was distilled off before use; b. p. 77—77·5°. Two spectrometers were used, details of which have been described in the previous papers. For the vapour, two absorption cells, 7 cm. and 21 cm. long, were used; for the liquid, layers about 0·1 mm. and 0·05 mm. thick were used.

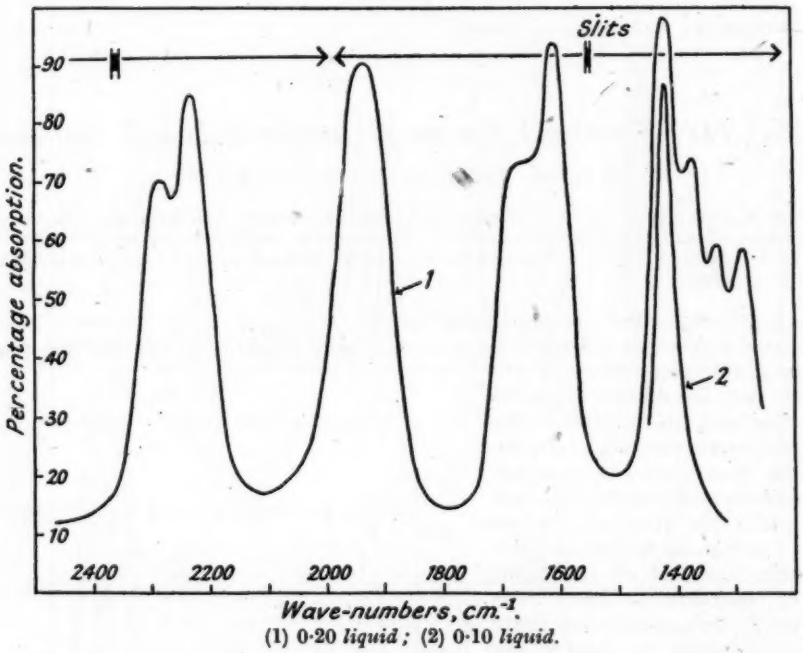
The sample of perbunan was a co-polymer of butadiene with acrylonitrile in the proportion 2 : 1. Films were made by the evaporation of solutions in ethylene dichloride from the surface of mercury. The spectra were measured immediately, since oxidation occurred fairly rapidly.

Results.—The spectrum of acrylonitrile vapour and of a thin film of liquid between 7 and 20μ is shown in Fig. 1, and that of the liquid between 4 and 8μ in Fig. 2. The positions in cm.$^{-1}$ of the absorption bands are summarised in Table I. The Raman data in this table were determined by Reitz and Sabathy (*Sitzungsber. Akad. Wiss. Wien*, 1938, IIb, **146**, 577).

TABLE I.

Infra-red spectrum. Vapour.	Infra-red spectrum. Liquid.	Raman spectrum. Liquid.	Infra-red spectrum. Vapour.	Infra-red spectrum. Liquid.	Raman spectrum. Liquid.	Infra-red spectrum. Vapour.	Infra-red spectrum. Liquid.	Raman spectrum. Liquid.
		238(7)		*ca.* 907		1412	1420	1406(4)
		305(1)	954	960 to 980	965(0)	1430	1610	1607(10)
		517(1)	971	1038			*ca.* 1650	
		561(3)					1938	
		628(1)	1086				2232	2224(10)
690		688(2)	1095	1097	1099(2)		2283	
	742		1105					2989(0)
782					1205(1)			
800	805			1288	1275(4)			
862				1330				
870	873	878(2)		1372				
880								

FIG. 2.



(1) 0·20 *liquid*; (2) 0·10 *liquid*.

DISCUSSION.

Acrylonitrile will have 15 normal modes of vibration. These can be analysed, to a first approximation, as follows. There will be 11 motions in the plane of the molecule and 4 out of the plane. Of the eleven planar modes, 5 will involve movements determined essentially by the skeleton C–C–C–N, and 6 will be largely determined by oscillations of C–H bonds. Of the four non-planar modes, one will be controlled by an oscillation of the skeleton and three by movements localised in the C–H bonds. The motions can then be described roughly as follows :

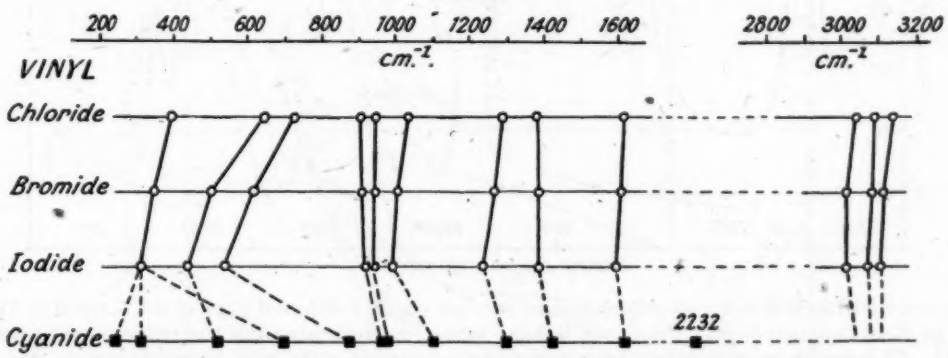
	Planar.	Non-planar.
3 C—H, 1 C=C, 1 C—C, 1 C≡N (valency vibrations.)	1 CH_2 deformation.	1 CH_2 bending.
	1 CH_2 rocking.	1 CH bending.
	1 CH rocking.	1 twisting.
	2 skeleton deformations.	1 skeleton bending.

We may assume as reasonable interatomic distances : $r_{CH} = 1{\cdot}08$ A., $r_{C=C} = 1{\cdot}35$ A., $r_{C-C} = 1{\cdot}46$ A., and $r_{CN} = 1{\cdot}16$ A., with angles of 120°. The principal moments of inertia are then 18, 170, and 188 $\times$ 10^{-40} g.-cm.^{2}, the least axis of inertia being slightly inclined to the direction of the C—C≡N part of the skeleton. The molecule will therefore approximate closely to being a symmetrical rotator, with two equal moments of inertia, and in Gerhard and Dennison's nomenclature (*Physical Rev.*, 1933, **43**, 197), $\beta \sim 9$. For the " parallel " type bands, in which the change of electric moment is parallel to the least axis of inertia, we shall expect absorption bands with three branches (P, Q, and R), the spacing between the pair of outermost maxima (P–R) being given by $[S(\beta)/\pi]\sqrt{kT/I_C}$. With a larger moment of inertia, 180 $\times$ 10^{-40}, this spacing is about 17 cm.$^{-1}$. The contour of the perpendicular type bands will show a strong central peak, flanked by shoulders of lower intensity. In reality, many of the oscillations will involve changes of electric moment with components along more than one axis of inertia, and the bands observed in these cases will therefore have a hybrid contour.

The infra-red band at 2232 cm.$^{-1}$ is, by analogy with other cyanides, attributed to the planar valency vibration connected with the C≡N link. Similarly, the band at 1610 is associated with the planar valency vibration of the C=C bond. In addition to these values, " coincidences " in the infra-red and Raman spectra are found with the infra-red bands 690, 870, 954, 971, 1095, 1288, 1420. These seven frequencies may be connected with fundamentals. Tentatively, we may assign 1413 to the planar CH_2 deformation, 1288 to the planar CH rocking mode, and 1095 to the planar CH_2 rocking mode. These values fall into line with those of similar vibrations in similar molecules. The contours of the bands at 954 and 971 show that they involve perpendicular type oscillations. These frequencies, moreover, correspond to the pair found at 909, 990 with hydrocarbons containing the vinyl radical (Thompson and Torkington, *loc. cit.*) and at 895, 940 with vinyl chloride. These can be attributed at once to bending motions of the CH_2 and CH radicals. The value 870 may be connected with the planar C–C bond valency vibration, but 690 cannot yet be assigned to a particular mode.

In addition to the above, there will be three valency vibrations associated with C–H bonds, all having values close to 3000 cm.$^{-1}$. This leaves three undetermined frequencies. Raman data show that all cyanides except methyl cyanide have a very low frequency of about 200. Hence 238 is probably a fundamental, and since it does not occur with (CH_3)—C≡N, it is perhaps the non-planar deformation of the C=C—C≡N skeleton. Similarly, 305 is probably a fundamental, and since no infra-red absorption could be detected at 561 and 628, whilst there are signs of feeble absorption at about 19μ (*ca.* 520 cm.$^{-1}$), 517 is taken as the other fundamental. Of the three unassigned fundamentals 305, 517, and 690, two are connected with planar rocking motions of the skeleton, and one is a twisting mode which will be largely determined by motions of the CH_2 about the double bond. It seems most reasonable to assign 305 to one of the rocking modes of the skeleton. Also, 690 is fairly intense in infra-red absorption and so it may not be due to the twisting mode. We should therefore assign 517 to the twisting mode, and 690 to the remaining skeleton deformation.

FIG. 3.



The band contours agree with this assignment. For instance, the bands at 954 and 970 are perpendicular in type, as would be expected for motions out of the plane of the molecule. The infra-red band at 870 is essentially " parallel," with roughly the correct spacing. It is primarily determined by a vibration of the C-C bond; the change of electric moment will have its greatest component along the least axis of inertia.

The above array of fundamentals also satisfactorily explains the other frequencies found in infra-red absorption and in the Raman spectrum, as shown in Table II. In Fig. 3, correlations are shown with the fundamental frequencies of the vinyl halides.

TABLE II.

Infra-red.				Raman.	
Frequency.	Interpretation.	Frequency.	Interpretation.	Frequency.	Interpretation.
742	970 − 238	*ca.* 1650	965 + 690	561	870 − 305
ca. 907	690 + 238		954 + 690	628	870 − 238
1038	2 × 517	1938	2 × 970	1205	971 + 238
1330	1095 + 238	2283	1420 + 870		
1372	2 × 690				
	1610 − 238				

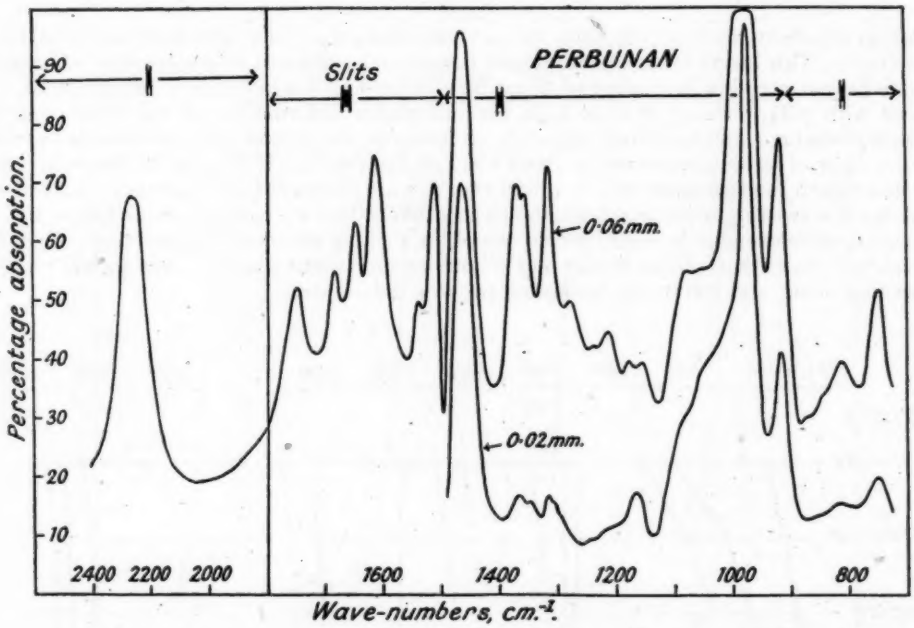
The spectrum of a sample of perbunan between 4 and 14μ is shown in Fig. 4. The most intense band is that at 970 cm.$^{-1}$. In the previous papers of this series the spectra of groups of olefinic hydrocarbons were described, from which it was found that characteristic absorption bands exist for the identification of the different classes. Thus, substances containing the vinyl radical have intense bands at about 909 and 990 cm.$^{-1}$, which also appear at slightly displaced frequencies in other vinyl compounds such as the halides. Olefins of the type R_1·CH:CHR_2, on the other hand, show a single strong band at about 965 cm.$^{-1}$. It is clear that the intense band with perbunan at 970 can similarly be attributed to the presence of a structure such as (I), which would arise from 1 : 4-addition of butadiene with acrylonitrile. Perbunan also has a weaker band at 915, and it is possible that any band at 990 would be submerged in the shoulder of the main band at 970. If

this were so, it would imply the presence of a structure such as (II), arising from 1 : 2-addition. We might therefore infer that with the sample examined here most of the polymerisation had proceeded by 1 : 4-addition,

but some by the other course. On the other hand, the interaction of vinyl radicals to form cross linkages would remove the bands due to these radicals.

The sample of perbunan shows a group of bands around 1600, the region of the characteristic C=C bond absorption. This may be consistent with the presence of the different types (I) and (II), and it is also possible

FIG. 4.



that ring closure within the molecule might lead to another slightly different type of C=C bond. The absorption band at 2260 connected with the C≡N linkage vibration is higher with the polymer than with acrylonitrile itself. This might be expected to arise owing to the removal of the neighbouring C=C bond; in methyl cyanide the frequency is about 2250.

The presence of the weak band at 1745 cm.$^{-1}$ suggests that a small number of carbonyl groups are present, probably introduced by rapid oxidation while the films were being made. More measurements on other samples and simpler related molecules are needed, however, before more precise deductions about the molecular structure can be made.

We thank the Royal Society and the Chemical Society for grants in aid of apparatus.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, March 21st*, 1944.]

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164. *The Structure of Polyisoprenes. Part III. Ultra-violet Absorption Spectra.*

By L. BATEMAN and H. P. KOCH.

The quartz ultra-violet absorption spectra of highly purified polyisoprenes correspond closely to those of simple ethylenes having the same degree of alkyl substitution at the double bond. This is also true of geranylamine hydrochloride, which shows no obvious characteristic that can be identified with the structural anomaly revealed by *X*-ray crystal analysis. The extent to which spectral variations are a measure of the electronic properties of groups and molecules of this type is therefore discussed—with the conclusion that for formally saturated substituents the correlation is still obscure. Evidence is presented to show that inductive influence is slight, and that interpretations hitherto advanced on the basis of hyperconjugation are unsound.

ULTRA-VIOLET absorption measurements on polyisoprenes were carried out in 1927 by Scheibe and Pummerer (*Ber.*, **60**, 2163), who compared the optical behaviour of rubber and gutta-percha with that of simple olefins. The considerable advances since made in correlating spectral data with molecular structure and in the theoretical

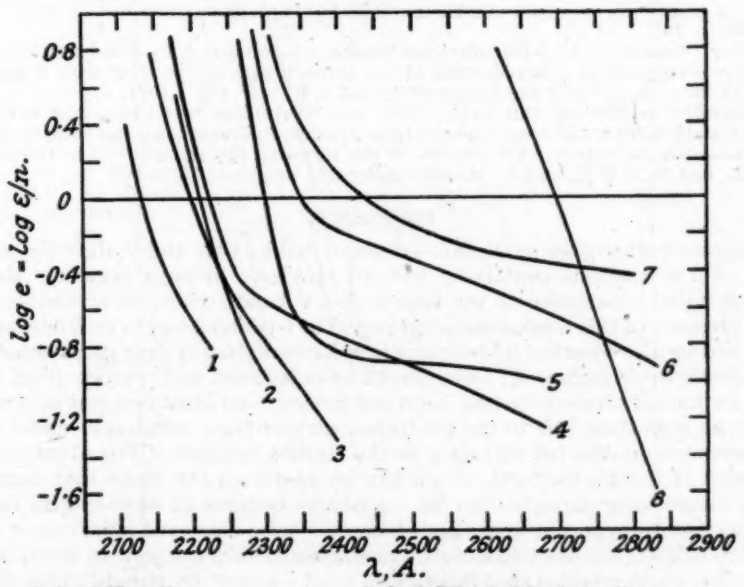
interpretation of the electronic bands, together with experimental progress in the preparation and purification of hydrocarbons, now make a fresh survey desirable. Additional justification is derived from the recent discovery, reported in Part I of this series, that the di-isoprene derivative geranylamine hydrochloride exhibits a new type of hybrid bond character akin to conjugation (Jeffrey, in the press; cf. Bateman and Jeffrey, *Nature*, **1943**, **152**, 446).

Isolated olefinic linkages give rise to intense absorption beginning in the neighbourhood of 2000 A. and rising steeply to a maximum near 1850 A., its precise location being governed by second-order environment effects (Carr and Walker, *J. Chem. Physics*, **1936**, **4**, 751; Price and Tutte, *Proc. Roy. Soc.*, 1940, *A*, **174**, 207). This characteristic absorption band has been identified by Mulliken (*Rev. Mod. Physics*, **1942**, **14**, 265) as an N→V transition from the normal to the first ionic excited state of the double bond. In conjugated systems it occurs at progressively longer wave-lengths, and in general, any change in electronic activation that affects the energy of the N→V transition will be reflected both in a displacement of the actual maximum and in a corresponding shift of the area covered by the absorption band. Since the polyisoprenes do not readily lend themselves to vacuum ultra-violet methods, our measurements were confined to solutions through quartz optics, a technique which fixes a lower wave-length limit of 2000 A. but offers the advantage of accurate intensity data in the accessible region of the steep near-ultra-violet slope of the spectrum.

Experimental.

Spectrographic Technique and Notation.—A small Hilger quartz spectrograph (E 484) was employed in conjunction with the Spekker photometer and a tungsten-steel spark source of ultra-violet light. The spectra were recorded on

Fig. 1.



1, 1 : 5-*Hexadiene*.
2, 1-*Pentene*.
3, 1 : 4-*Pentadiene*.
4, cyclo*Hexene*.
5, 2 : 6-*Dimethyl*-2 : 6-*octadiene*.
6, 1-*Methyl*cyclo*hexene*.
7, *Rubber* (*in* C_6H_{12} *containing* 10% EtOH).
8, *Isoprene*.

Kodak B-10 plates, and the match-points determined visually. Except where otherwise stated, pure *cyclo*hexane was used as the solvent in cell lengths of 0·1 to 5·0 cm. Independent determinations carried out on separate samples of the same hydrocarbon provided confirmation that the probable error was less than 3%, which is negligible on the steep portion of the absorption slope.

The molecular extinction coefficient ε is defined by $\varepsilon = (M/lc)\log_{10}I_0/I$, in which $\log_{10}I_0/I$ at the matching wave-length is given directly by the drum-setting of the photometer after allowance for a suitable blank; l is the cell-length in cm., and c the concentration (in g./l.) of the dissolved substance of molecular weight M. The ethylenic extinction coefficient $\epsilon = \varepsilon/n$ is also employed in the study of the polyisoprenes and other compounds containing n double bonds in order to obtain comparable intensity values representing the absorption of one ethylenic linkage. With this convention the absorption of rubber is plotted per single isoprene residue, but that of isoprene itself as the absorption of the half-molecule.

Preparation and Purification of Materials.—1-tert.-*Butyl*cyclo*hexene* is the only new compound to be described, but details are also given of the purification procedures adopted for those hydrocarbons whose low-intensity absorption bands are plotted in Fig. 1. The preparative methods employed for the remaining materials not specially purified for low-intensity investigation are briefly summarised at the end of this section.

1-tert.-*Butyl*cyclo*hexene*.—The reaction of *tert.*-butylmagnesium chloride with *cyclo*hexanone produced much undesired *cyclo*hexanol (b. p. 61°/13 mm.) and a poor yield of 1-tert.-*butyl*cyclo*hexanol* (b. p. 80°/13 mm.), which were separated in a Dufton column. This carbinol solidified almost immediately in the receiver (m. p. 49—50°) but was too soluble in the usual solvents to permit of recrystallisation (Found: C, 76·8; H, 12·9. $C_{10}H_{20}O$ requires C, 76·95; H,

12·8%). Distillation of this from a few crystals of iodine readily gave 1-*tert.*-butyl*cyclo*hexene (b. p. 158°/765 mm.), which was kept over molten sodium for one hour and finally redistilled at 51°/14 mm.; $n_D^{19\cdot5°}$ 1·4632 (Found: C, 86·8; H, 13·2. $C_{10}H_{18}$ requires C, 87·0; H, 13·0%).

Spectrographically Pure Hydrocarbons.—Except where otherwise stated, each specimen was distilled through all-glass, grease-free, fractionation apparatus of the Fenske–Whitmore type immediately before optical examination.

1-Pentene and 1 : 4-pentadiene were generated from their pure bromo-ethers which had been obtained by the method of Boord *et al.* (*J. Amer. Chem. Soc.*, 1930, **52**, 3396; 1931, **53**, 1505) as modified by Kistiakowsky *et al.* (*ibid.*, 1936, **58**, 146). The hydrocarbon spectra underwent no further change after three azeotropic distillations with methyl alcohol (b. p. 26·6$_5$° and 23·5$_0$°, respectively), and the pure olefins boiling at 30·1$_5$° and 25·8$_0$° were isolated by repeated washings with ice-water.

The low-intensity absorption of 1 : 5-hexadiene, prepared from allyl bromide and magnesium, remained constant after three fractionations at 59·1°. Isoprene was similarly purified (b. p. 33·87°/758 mm.) from the crude hydrocarbon obtained on alkaline distillation of its recrystallised sulphone (m. p. 63·5°).

None of the *cyclo*hexenes could be freed from traces of conjugated dienes by fractionation alone, but both *cyclo*hexene and 1-methyl*cyclo*hexene were produced spectrographically pure on treatment with maleic anhydride (Stücklen, Thayer, and Willis, *ibid.*, 1940, **62**, 1717).

"Dihydromyrcene" (Semmler and Mayer, *Ber.*, 1911, **44**, 2010) has been employed in chemical work as a representative of the di-isoprenic 2 : 6-dimethyl-2 : 6-octadiene hydrocarbon (Farmer and Sutton, J., 1942, 139; Bloomfield, this vol., p. 114), but Dupont and Desreux (*Bull. Soc. chim.*, 1937, **4**, 422) obtained Raman spectra evidence that the reduction of β-myrcene invariably results in a certain amount of 1 : 2- as well as 1 : 4-addition of hydrogen. Apart from this objectionable complication, the spectra of our dihydromyrcene samples also exhibited the typical aromatic band system of *p*-cymene (cf. Bradley and Richardson, *Ind. Eng. Chem.*, 1940, **32**, 963), an impurity which could not be removed by fractionation. 2 : 6-Dimethyl-2 : 6-octadiene was therefore made by the reduction of purified geraniol with sodium in liquid ammonia (Chablay, *Ann. Chim.*, 1917, **8**, 145; Dupont, Dulou, and Desreux, *Bull. Soc. chim.*, 1939, **6**, 83), and we are indebted to Dr. F. Hilton for this preparation. On careful fractionation, the pure hydrocarbon distilled at 61·2°/16 mm.; $n_D^{19\cdot5°}$ 1·4498.

Rubber hydrocarbon was purified down to constant low-intensity absorption by a special precipitation method of fractionation, details of which will be given elsewhere. The final specimen contained N, 0·01% and had a viscosity molecular weight of 330 × 10³.

Preparation of Other Materials.—1 : 2-Dimethyl*cyclo*hexene was obtained by condensation of methylmagnesium iodide with 2-methyl*cyclo*hexanone and dehydration of the tertiary carbinol product with iodine. After purification *via* the crystalline dibromide (m. p. 142°), the hydrocarbon had b. p. 135°, $n_D^{21°}$ 1·4591.

Geranylamine hydrochloride (Sutton, this vol., p. 306) was crystallised four times from acetone (m. p. 146°) and dried in a vacuum. Oxidation impurities were removed from squalene hydrocarbon by adsorption on a column of alumina. Pure white Tjipetir gutta-percha, obtained by courtesy of the Research Department of the Telegraph Construction and Maintenance Co., Ltd., had N, 0·01%, and a viscosity molecular weight of 78 × 10³.

Discussion.

Low-intensity Long-wave Absorption of Olefins.—It was noted by Carr and Walker (*loc. cit.*) that even highly purified specimens of hydrocarbons containing isolated ethylenic linkages regularly showed characteristic long-wave absorption tails in addition to the intense N→V bands occurring at shorter wave-lengths. We have confirmed the presence of this weak absorption region in 1-pentene and in *cyclo*hexene (Stücklen, Thayer, and Willis, *loc. cit.*), and we also observed its existence in spectrographically pure preparations of 1 : 5-hexadiene, 1 : 4-pentadiene, 1-methyl*cyclo*hexene, 2 : 6-dimethyl-2 : 6-octadiene, and rubber (Fig. 1). The electronic process responsible for the long-wave ethylenic band has not yet been identified, but is of real significance as it must evidently play an important rôle in the photochemistry of these substances under sunlight conditions. Carr and Walker have already directed attention to the marked increase of this absorption region associated with alkyl substitution of the double bond, and it can be seen from the figure that both methyl*cyclo*hexene and rubber actually absorb more strongly than the conjugated isoprene at wave-lengths longer than 2750 A.

Most of the olefinic spectra reported from Carr's laboratory also displayed inflexions or step-outs of varying intensity in the region of 2300 A. We encountered similar features in our own hydrocarbon specimens before systematic fractionation which revealed that this type of band is caused by minute traces of intensely absorbing contaminants of a conjugated diene structure. Such irregularities are therefore not to be regarded as characteristic of pure olefin spectra, as was indeed suspected by the American authors.

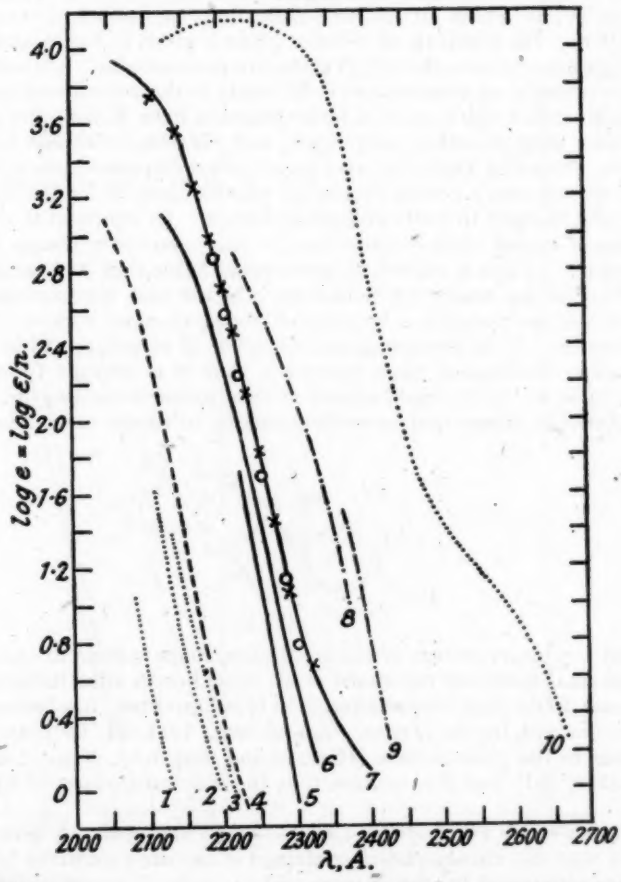
Classification of Intense Polyisoprene Absorption.—The extreme quartz ultra-violet spectrum of the polyisoprenes is compared with that of some related olefins in Fig. 2. The complete coincidence of the absorption curves of rubber and gutta-percha is of interest in view of the geometrical isomerism which is believed to distinguish these two hydrocarbons. Ramart-Lucas (Grignard, "Traité de Chimie Organique," 1936, II, 59) has, however, already refuted earlier assertions that there existed a systematic difference between the ultra-violet spectra of *cis–trans*-isomeric absorbing groups, and the high-intensity N→V absorption of the two forms of 2-butene appears to occur at the same wave-lengths (Carr and Stücklen, *J. Chem. Physics*, 1936, **4**, 760). Most of the existing spectrographic data on pairs of geometrical isomers relate to more complex chromophores than the simple alkyl-substituted ethylenic linkage, and the reduced absorption usually displayed by the *cis*-isomerides can be attributed to their shortened spatial extension or to steric interference between *cis*-ethylenic substituents (Koch, *Chem. and Ind.*, 1942, **61**, 273). The polyisoprene curve also covers our measurements on squalene and is identical with the earlier data on rubber and gutta-percha obtained by Scheibe and Pummerer (*loc. cit.*), whose curve for diallyl is likewise confirmed.

The figure shows that the spectra of the polyisoprenes and other unsaturated hydrocarbons of the tri-substituted type $CR_1R_2{:}CHR_3$ form a well-defined group, clearly differentiated from all other ethylenic compounds, which are either more or less absorptive in accordance with the extent of substitution on the double bond. The precise nature of the alkyl substituents appears to be largely immaterial in this classification pro-

vided that no conjugation occurs when more than one double bond is present in the molecule (cf. spectrum of isoprene). Carr and Walker (*loc. cit.*) and Price and Tutte (*loc. cit.*) previously observed corresponding red shifts in the vapour spectra of some simple ethylenes in the vacuum ultra-violet. Analogous long-wave alkylation displacements are also known to occur in the spectra of the conjugated dienes (Price and Walsh, *Proc. Roy. Soc.*, 1940, *A*, **174**, 220; Booker, Evans, and Gillam, J., 1940, 1453) and of olefinic centres conjugated with a carbonyl group (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123).

Although the absorption of 1 : 5-hexadiene at the extreme short-wave end of the quartz ultra-violet is in line with this classification, yet the spectra of the monosubstituted ethylenes 1-pentene and 1 : 4-pentadiene appear to lie remarkably close to the curve of *cyclo*hexene, which is more highly substituted on the double bond.

FIG. 2.

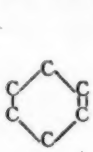


1, 1 : 5-*Hexadiene.*
2, 1 : 4-*Pentadiene.*
3, 1-*Pentene.*
4, cyclo*Hexene.*
5, 2 : 6-*Dimethyl*-2 : 6-*octadiene.*
6, 1-*Methyl*cyclo*hexene.*
7, *Rubber* (*in* C_6H_{12} *containing* 10% EtOH).
× × ×, *Gutta-percha.*
○○○, *Squalene.*
8, 1 : 2-*Dimethyl*cyclo*hexene.*
9, *Tetramethylethylene* (*after Carr and Walker*).
10, *Isoprene.*

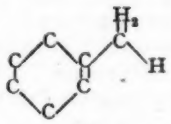
According to Carr and Walker, who record different absorption values for 1-pentene, *iso*propylethylene is even more absorptive than *cyclo*hexene in this region. Since the peak of the *iso*propylethylene band is reported to fit normally into its group position (Carr and Stücklen, *loc. cit.*), it seems possible that the irregular spreading-out of the monosubstituted ethylene absorption curves may be due to a peculiar broadening or intensification of the band rather than a genuine wave-length shift.

Alkyl Shifts and Hyperconjugation.—Mulliken (*J. Chem. Physics*, 1939, **7**, 339) developed the theory of hyperconjugation to account for the abnormal long-wave absorption of cyclic conjugated dienes, and used it subsequently to explain the successive absorption shifts effected by alkyl substitution in simple ethylenes. The theory has been generalised and expressed quasi-quantitatively in quantum-mechanical terms, although some of the original views have been drastically revised (Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41). Hyperconjugation, which is now considered to find expression in the properties of the ground state rather than those of excited states, is still regarded as determining the red shifts, although decreases in ionisation potential are mainly attributed to charge transfer (Mulliken, *Rev. Mod. Physics*, *loc. cit.*). Since the

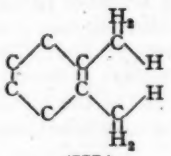
conjugative powers of saturated bond electrons with unsaturated centres is much greater for C–H than for C–C bonds, the long-wave displacements in the *cyclo*hexene series are due, on this view, to the increasing conjugation inherent in structures (I)—(III). We have been able to test this theory experimentally by examining



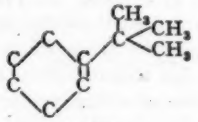
(I.)



(II.)



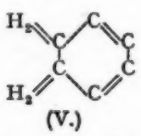
(III.)



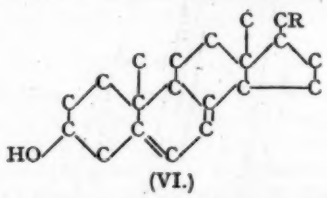
(IV.)

1-*tert.*-butyl*cyclo*hexene (as IV) in which all the side-chain hydrogen atoms necessary for hyperconjugation have been replaced by carbon. The spectrum of this new olefin is given in Fig. 3, and comparison with methyl*cyclo*hexene and other *cyclo*hexenes proves that alkyl shifts are predominantly a function of carbon substitution as such, irrespective of the presence or otherwise of C–H bonds in the substituent group. This result is comparable with Conant and Kistiakowsky's heat of hydrogenation data (*Chem. Rev.*, 1937, **20**, 181) in which negligible differences between methyl-, ethyl-, *iso*propyl-, and *tert.*-butyl-ethylene were found.

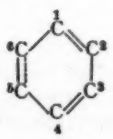
Differing from Mulliken, Price and Tutte (*loc. cit.*) regard alkyl displacements as chiefly due to a reduction in ionisation potential of the ethylenic centre by charge transfer from the adjacent alkyl groups, a process which should lead to parallel changes in heats of hydrogenation. In conjugated *cyclo*hexadiene the $N \rightarrow V_1$ transition occurring at much longer wave-lengths than in the open-chain dienes is similarly related to an alteration in the ground state. If this is correct, it seems remarkable that its heat of hydrogenation does not differ appreciably from that of an analogous butadiene (Conant and Kistiakowsky, *loc. cit.*). Mulliken's alternative explanation of the *cyclo*hexadiene spectrum is open to more serious objection from arguments based on chemical constitution. If hyperconjugation depicted in structure (V) is regarded as determining the red shift from the normal conjugated diene spectrum, then it is difficult to see why substituted *cyclo*hexadienes of the type of ergosterol (VI) should absorb at even longer wave-lengths. In point of fact, all the spectrographic data on polycyclic dienes that have accumulated in recent years (Booker, Evans, and Gillam,



(V.)



(VI.)



(VII.)

loc. cit.) serve to show that the incorporation of the conjugated diene system in one six-membered ring is the exclusive cause of the abnormal spectrum regardless of all second-order substitutional influences.

It has been shown beyond doubt that hyperconjugation is an important mechanism of electronic activation in chemical processes (Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657), and physical measurements have indicated its influences in the ground state (Hannay and Smyth, *J. Amer. Chem. Soc.*, 1943, **65**, 1931; Baker and Hemming, J., 1942, 191), but it is evident that the spectral features of hyperconjugation have yet to be correctly described.

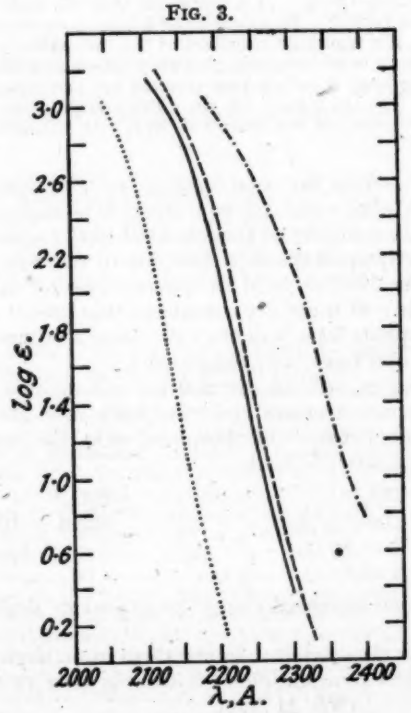
Interaction of Double Bonds in the Polyisoprene Chain.—There is a generally accepted working hypothesis in ultra-violet spectroscopy that two chromophores contained in the same molecule behave as separate absorbing entities provided they are separated by one or more carbon atoms (Ramart-Lucas, *loc. cit.*). This is borne out by our data on 1 : 4-pentadiene, 1 : 5-hexadiene, and the polyisoprenes, all of which fall into their normal group classification in accordance with the degree of alkyl substitution of the double bond. The spectrographic rule is paralleled by the available thermal data, since the heat of hydrogenation of 1 : 5-hexadiene is almost identical with twice that of a singly substituted ethylene, and the same is very nearly true of 1 : 4-pentadiene (Kistiakowsky *et al.*, *loc. cit.*). The only exception that might be quoted against this generalisation is the spectral anomaly of the cyclic conjugated dienes. Although Price and Walsh (*Proc. Roy. Soc.*, 1941, *A*, **179**, 201) tentatively postulated electronic repulsion between the two *cis*-linked double bonds, or, alternatively, the existence of Dewar type resonance structures in 1 : 3-*cyclo*hexadiene, yet Woodward (*J. Amer. Chem. Soc.*, 1942, **64**, 72) envisaged an incompletely insulating 5 : 6 single bond in a benzene-analogous structure (VII). This formulation would account for the long-wave absorption, but the normal heat of hydrogenation remains a difficulty.

Recent physical evidence points to incomplete insulation of the 1 : 5-spaced double bonds in the polyisoprene chain, comparable with that represented in structure (VII). *X*-Ray analysis of the di-isoprene derivative geranylamine hydrochloride, $CMe_2{:}CH{\cdot}CH_2{-}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}NH_2,HCl$ (Jeffrey, *loc. cit.*), has revealed a significant shortening of the central single bond accompanied by a planar arrangement of the adjacent groups. It has been suggested (Bateman and Jeffrey, *loc. cit.*) that this unique bond character, which simulates normal conjugation, is the result of hyperconjugation. The ethylenic centres are considered to promote hybridisation which partially localises the C–H bond electrons of the central CH_2 groups in the hybrid bond. It is perhaps

surprising therefore that the N→V band of the polyisoprenes does not reflect this structural modification and that the spectrographic insulation rule still holds. There is no difference in this respect between di-isoprene itself and its amine hydrochloride, whose spectra are plotted side by side in Fig. 4. Since saturated amine hydrochloride groups are completely transparent in the quartz ultra-violet, the absorption of geranyl-amine hydrochloride in this region is determined exclusively by the di-isoprene system, and the close coincidence of the two spectra is very striking.

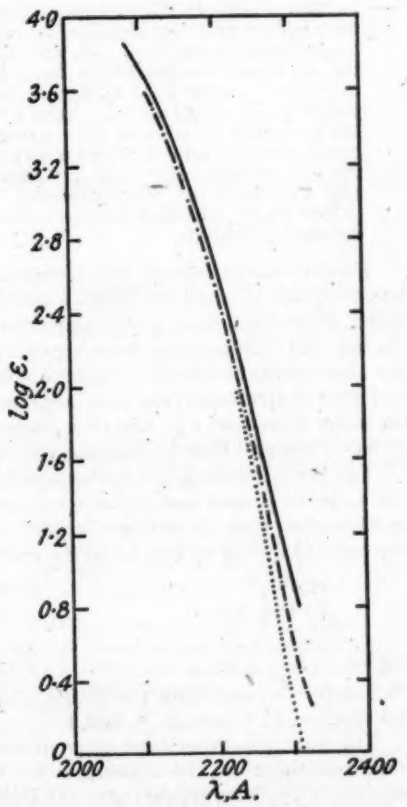
The latter observation is of further interest owing to its bearing on the inductive dependence of N→V transitions (cf. Jones, *Chem. Rev.*, 1943, **32**, 14). Price and his colleagues conclude that the determinative function of alkyl substituents at ethylenic centres is one of charge transfer, which they identify with the inductive mechanism well recognised chemically. Now, it is well known that a substantial fraction of the electrostatic force of an ionic pole is transmitted through one saturated carbon atom. Hence at the nearer

FIG. 3.



..... cyclo*Hexene.*
——— 1-tert.-*Butyl*cyclo*hexene.*
– – – – 1-*Methyl*cyclo*hexene.*
—·—·— 1 : 2-*Dimethyl*cyclo*hexene.*

FIG. 4.



——— *Geranylamine hydrochloride (di-isoprene amine hydrochloride) in* EtOH.
—·—·—· 2 : 6-*Dimethyl*-2 : 6-*octadiene (di-isoprene) in* EtOH.
..... 2 : 6-*Dimethyl*-2 : 6-*octadiene (di-isoprene) in* C_6H_{12}.

double bond in geranylamine hydrochloride there will be an added inductive influence of marked strength directively the same as that of the methyl substituent. Moreover, it is not possible in this case to invoke an alternative and compensating mode of polarisation as in *cis*-dichloroethylene and chloroprene, where correlation between spectral displacement and the inductive power of the chlorine atom was also absent (Price and Walsh, 1940, *loc. cit.*), and we must conclude that double bond absorption is far less sensitive to inductive influence than hitherto believed.

There appear to be three possible explanations why the spectrum of geranylamine hydrochloride shows no departure from that typical of a substituted ethylene in spite of the unusual character of the central single bond. First, the abnormal bond may be peculiar to the crystalline state; secondly, the presence of the ethylenic centres may not in fact govern the new hybridisation. We see no reason for accepting the former, and regard the latter as improbable. Thirdly, both normal and excited states of the double bond may participate equally in the hyperconjugation process, in the same way, presumably, as they are similarly responsive to the polar force of the ammonium group. However, this problem of the unchanged transition energy must

remain unsolved until the true spectral consequence of hyperconjugation is elucidated, and the nature of the unusual hybridisation more fully understood.

Our thanks are due to Dr. D. A. Sutton for supplying samples of dimethyl*cyclo*hexene and squalene for this investigation, which forms part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

48, Tewin Road, Welwyn Garden City, Herts. [*Received, July 6th*, 1944.]

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165. *Diffusion Potentials and Mobilities of Multivalent Ions: Potassium Ferricyanide and Ferrocyanide.*

By E. B. R. Prideaux.

The potentials, E_d, at various kinds of liquid junction between solutions of potassium sulphate, potassium ferricyanide and ferrocyanide, severally, have been determined by various methods. These potentials are proportional to log C_I/C_{II}, C_I and C_{II} being the concentrations. When extrapolated to zero concentration, the E_d values for potassium ferri- and ferro-cyanide are nearly equal, and the transport numbers t_- and mobilities l_- are in good agreement with those determined by conductivity. It is confirmed that the equivalent mobilities $_0l_-$ of $\frac{1}{4}[Fe(CN)_6]^{4-}$ and $\frac{1}{3}[Fe(CN)_6]^{3-}$ are in the ratio 1·11 : 1. In solutions of higher concentration, the E_d values for the two salts diverge and are so related that the transport numbers of the two salts become equal when the concentration is 0·1N; beyond this, the value for the ferrocyanide probably falls below that for the ferricyanide. The data are interpreted on the assumption that the only ions present are the potassium and the ferro- or ferri-cyanogen. Calculations based on the existence of an intermediate ion, *e.g.*, $[KFe(CN)_6]^{3-}$, although satisfactorily explaining the t_- and λ values, do not accord so well with the observed diffusion potentials.

Proportionality between Ion Mobilities and Charges.—It follows from the usual representation of ionic motions by the equation based on Stokes's law that, all other conditions being equal, the equivalent ionic mobility of the multivalent ion will be proportional to the total charge, and the mobility of the ion itself to the square of the charge. The difficulty of proving this proposition depends partly upon the fact that only in very special cases are the conditions equal. Stokes's law can probably only be regarded as valid for spheres of radius $>10^{-6}$ cm., and most simple ions of low molecular weight are smaller than this. It is usually considered that ions of virtually the same structure, *e.g.*, the phosphate and the hydrogen phosphate ions, will obey the same modified form of Stokes's law and thus be comparable; and actually only such ions have been compared.

The conductivities of various alkali and ammonium phosphates, and the distribution of ammonia between the aqueous phases and chloroform, were used to determine concentrations and eventually mobilities of the participating ions, as well as the first and the second dissociation constant of phosphoric acid, the third being less easy to define by conductivity methods. The limiting conductances were:

$H_2PO_4^{1-}$	HPO_4^{2-}	PO_4^{3-}	$P_2O_7^{4-}$
26·4 ± 1·0	106·8 ± 2	205·0 ± 30	325·6 ± 10
	$\frac{1}{2}$ = 53·4	$\frac{1}{3}$ = 69·0	$\frac{1}{4}$ = 81·4
Factor	2·02	2·60	3·08

The factors representing the ratios of increase of mobility due to increased charge progressively depart from the theoretical values, 2, 3, and 4.

The fourth hydrogen ion of pyrophosphoric acid is even less dissociated than the third of orthophosphoric acid, and therefore the correction for hydrolysis, *e.g.*, of sodium pyrophosphate is even greater (a 0·0003M-solution is 7% hydrolysed; Abbott and Bray, *J. Amer. Chem. Soc.*, 1909, **31**, 729).

A greater choice of anions is afforded by polycarboxylic acids. For instance, the conductivities of the penta- and tetra-sodium salts of benzenepentacarboxylic acid were determined at 25° by Noyes and Lombard (*ibid.*, 1911, **33**, 1423). Ionic conductances of $C_{11}HO_{10}^{5-}$ and $C_{11}H_2O_{10}^{4-}$ were 496 and 332 respectively, ratio 1·49; whereas the theoretical ratio $5^2/4^2$ is 1·56. The first dissociation of the free acid is practically complete at a concentration of 6 millimols. per 1000 g. of water.

Essential material for an investigation of this subject is furnished by highly dissociated salts of tervalent and quadrivalent strong acids. The ferro- and ferri-cyanides fulfil these conditions, and possess the further advantage that their conductivity data are almost completely available.

Symbols used are those given in the Report of the Joint Committee of the Physical Society, the Faraday Society, the Chemical Society and British Chemical Abstracts, unless otherwise stated. For the equivalent ionic conductances or ionic mobilities, l_- and l_+, there are substituted sometimes (*i.e.*, in ratio terms from which F' cancels) the velocities u and v; t_+ and t_- denote the transport numbers of cation and anion. $E_{I\rightarrow II}$ is the diffusion potential between solutions having concentrations C_I and C_{II} ($C_I > C_{II}$) and is taken as positive when side I is positive to II.

A selection of the equations applicable to the present cases is as follows:

$$t_+ = l_+/(l_+ + l_-),\ t_- = l_-/(l_+ + l_-) \text{ or } v/(u+v) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or, in case several kinds of ions are present:

$$t_- = \Sigma v_i C_i/(\Sigma u_i C_i + \Sigma v_i C_i) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The change of t with concentration is given by an equation derived from that of Onsager by Hartley and Donaldson (*Trans. Faraday Soc.*, 1937, **33**, 457) *viz.*,

$$dt_-/(d\sqrt{C}) = (21{\cdot}14/\lambda)(z_-t_+ - z_+t_-)\sqrt{z_+ + z_-} \text{ as } C \to 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The diffusion potentials are given by the general equation

$$E_{I \to II} = \text{constant} \times T\left(\sum \frac{t_-}{z_-} - \sum \frac{t_+}{z_+}\right) \log \frac{a_I}{a_{II}} = 0{\cdot}0591 \frac{z_+v - z_-u}{z_+z_-(u+v)} \log \frac{a_I}{a_{II}} \quad . \quad . \quad . \quad . \quad (4)$$

in which the a's may be the activities determined by various methods, but in the present work are usually concentrations C expressed in g.-equiv./l. The second part refers to two kinds of ion of valencies, z_+ and z_-.

If n_+, n_-, and n are the numbers of cations, anions, and ions of both kinds, respectively, produced by the dissociation of 1 mol. of the salt, then the relation between the transport number factor $f(u, v, z)$ or $f(t_-, z)$ and the transport number t_- is

$$f(t_-, z) = (t_-n/n_+ - 1)/z_+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In the electrolytes under consideration, $z_+ = 1$ and $n = z_- + 1$, also $n_+ = z_-$. Therefore

$$f(t_-, z) = t_-(z_- + 1)/z_- - 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

in which the subscripts may be omitted from z.

In all cases where $z_- = 2$, 3, or 4, $f(t_-, z)$ is negative, and therefore $E_{I \to II}$ is negative, for although v may be greater than u, it is never greater than or equal to zu [equation (4)].

Experimental.

Liquid junctions of various types were measured in symmetrical chains or combinations of solutions contained in specimen tubes or salt-bridges and terminating in symmetrical half-cells which were the saturated (more rarely, x) potassium chloride–calomel–mercury type. These were connected by salt-bridges of the same potassium chloride solutions with guard tubes I*a* and II*a*, then came tubes I and II, between which was the liquid junction (broken line). Elimination of diffusion potentials by saturated potassium chloride salt-bridges is denoted by double lines as usual:

Hg, HgCl, KCl|KCl||I*a*|I¦II|II*a*||KCl, HgCl, Hg

The equality of the electrodes was tested occasionally by connecting them directly, and that of the whole combination by substituting a saturated potassium chloride salt-bridge for the liquid junction. This does not, of course, reveal the existence or otherwise of a *P.D.* between saturated potassium chloride and I*a*, which was, however, investigated by a special method described below.

The apparatus for static junctions was set up in an air thermostat. A double-walled, copper water-bath (dry) was heated at the bottom and sides by resistance elements, the current being controlled by a vacuum switch and bimetallic spiral. The air in the box was stirred by a fan inserted through the roof. Temperature between the walls was auto-regulated over a small range round 25°. During an experiment, it was hand-regulated between about 24° and 26°, and the temperature of the enclosed liquids was also maintained at 25°±1°.

The Liquid Junctions: Types of Apparatus.—Conditions for forming satisfactory liquid junctions have been discussed by Guggenheim (*J. Amer. Chem. Soc.*, 1930, **52**, 1315), Guggenheim and Unmack (*Kgl. Danske Videnskab. Selskab. Math.-fys. Meddelelser*, x, 8, 1930), and many previous investigators. Free-diffusion and continuous-mixture junctions were compared. In the former type the most important requisite for reproducibility is cylindrical symmetry within a tube. This was realised by drawing a solution up into the tube, which usually gave results reproducible to a few tenths of a millivolt in the case of the uni-univalent electrolytes investigated. A method which is said to give the best reproducibility is to run in the more concentrated solution I below a tap of the same bore as the tube, to close the tap, wash out the space above it, and then pipette in solution II. Satisfactory static junctions were obtained in the present work by preparing a solution bridge of II, one end of which was lightly plugged with cotton-wool or glass-wool, and immersing the two limbs slowly and uniformly in two tubes containing solutions I and II, the levels of which had been carefully adjusted so that the junction rose for a short distance. Potentials were established almost at once; usually they remained constant for hours with the higher concentrations, or faded out in ½ hour with the very low concentrations. It is well known that potentials of the *C* I, *C* II type are steadier than any other kind, and are mostly independent of the kind of junction (free-diffusion or continuous mixture); but in the case of the present unsymmetrical salts, variations in the static junctions are sometimes found, and these may depend on the degree to which the junctions at the moment of setting up approximate to one or other of these two types. If so, these variations certainly persist in any one experiment. For these and other reasons, it was considered desirable to carry out parallel experiments with flowing junctions.

Apparatus for Flowing Junctions.—The apparatus of Ferguson, Van Lente, and Hitchens (*J. Amer. Chem. Soc.*, 1933, **54**, 1285) consists of a very large three-way tap, the bore of which is the same as that of the inlet tubes of the two solutions and the outlet tube containing the liquid junction. The inlet tubes dip into two reservoirs containing solutions I and II at the same level. Tube I is first filled, above the tap, which is then turned, putting into communication solution II, which washes out the upper part. After adjustment of the reservoirs, the tap is turned back, establishing the junction without disturbance. On opening the outlet, a liquid junction is formed. Thus, either type of junction can be established at will, and can be preserved for long periods. This apparatus gives excellent results and requires only moderate quantities of solution. It is not very convenient for use in a thermostat.

Another form is that due to Scatchard (*J. Amer. Chem. Soc.*, 1925, **47**, 641, 698). The graduated reservoirs, side tubes, and outlet tube form one piece of robust construction, suitable for immersion in a thermostat. Solutions I and II are separated initially by a rubber stopper carried on a vertical glass rod. The stopper is first pressed down on to an accurately formed constriction. After the reservoirs have been levelled, the stopper is slowly raised and a wide static junction is established. This is converted into a flowing one by gradually opening the outflow tube, so that about 1 drop falls in 2—5 seconds. By this means static and flowing junctions can be measured at will. In the present series they were identical. As in the preceding form of apparatus, if the junction has been badly made or become mixed, it usually cannot be restored without emptying and refilling the apparatus. It also requires a large volume of solution,

which is somewhat reduced, however, by placing ballasted tubes in the reservoirs. Probably on account of its great area, this is the most reliable and reproducible of all liquid junctions, and is especially suited to pairs of solutions with a considerable difference of concentration, but less suited to very dilute solutions. Occasional high results, noticed in the static junctions, do not occur. On the other hand, potentials may be too low on account of mixing at the large surface, and soon fall when this becomes static, to rise again when the flow is resumed at the minimum rate mentioned above.

Roberts and Fenwick's junction (*ibid.*, 1927, **49**, 2787) is formed by allowing films of solutions I and II to stream past the opposite sides of a hole of about 1 mm. diameter, pierced in a vertical sheet of mica. The streams are directed down channels in the paraffined surface so as to form drops which must fall at about the same speed from separate points. This method requires delicate manipulation, and the directions given must be carefully observed. There are several sources of error and the apparatus is capable of improvement. Some satisfactory results, however, were obtained, which have some value as confirming those gained by the other methods. The flowing junctions, except that of Scatchard, were not thermostatically controlled, but were at room temperature, 16—20°.

Salt Solutions.—Potassium sulphate solutions were made from the "AnalaR" salt, and measurements carried out as above. Potentials were steady.

Potassium ferricyanide solutions were made from the "A.R." salt in good distilled water, the higher dilutions with conductivity water. On account of their instability, solutions should not be too old, but storage for several weeks in the dark does not affect the potentials. Solutions of about M/30-concentration show a slight precipitate, resembling ferric hydroxide, on long keeping, but this was absent from more concentrated or more dilute solutions. This is probably produced as a further stage of the first hydrolysis: $[Fe(CN)_6]^{3-} \rightarrow [Fe(OH)(CN)_5]^{3-} + HCN$. If the first stage is reversible, it might account for the uncertainty in potentials referred to below. Concentrations were sub-multiples of M/3 = 1·0N, and usually of M/30, the lowest being M/3000. Concentration ratios were usually 10/1, but sometimes 5/1, 20/1, or 50/1; the results usually showed a satisfactory agreement with the logarithmic law, and also suggested that, for purposes of computation, concentrations rather than activities should be used. One particular range, M/30—M/300, gave results which were less constant and more influenced by change of apparatus than any other pair. However, the apparatus with wide junction (Scatchard) gave a very steady 17 mv., which was taken as the most probable value.

Potassium ferrocyanide solutions were made from a good commercial salt which had been checked by analysis, and also from "A.R." reagent. They were made with distilled water, and in the higher dilutions with conductivity water. Concentrations were M/8 and M/20, but chiefly M/40 (=0·1N) and sub-multiples, the lowest being M/4000. Ratios of 10/1, 5/1, 20/1, and 50/1 were used, and the logarithmic law of concentrations was confirmed.

Potassium ferrocyanide is slightly hydrolysed in solution. When freshly made, solutions are neutral (to neutral-red), but in about 15 minutes they become alkaline (to phenolphthalein) (Kolthoff, *Z. anorg. Chem.*, 1920, **110**, 143). The hydroxyl-ion concentration corresponding to each solution may be estimated, from the fourth dissociation constant ($-\log K_4 = 4{\cdot}237$ at C 20·1; Kolthoff and Tomsicek, *J. Physical Chem.*, 1935, **39**, 955) and pK_w at 18° = 14·27, to be 3×10^{-6}. In any case, this concentration is of a lower order than those of the other ions.

An M/40-solution which had been kept stoppered for some months gave a decided pink reaction with saturated phenolphthalein solution, but solutions of M/80 or lower concentration showed no colour.

Test for an Extra Diffusion Potential.—Attention has been directed above to the possibility of a diffusion potential at the junction between a saturated potassium chloride salt bridge and solution I when this is of the order of 0·1N or more. An attempt was made to evaluate this as follows. Potential differences were measured between smooth platinum electrodes, which function as oxidation–reduction electrodes in solution I, and the saturated calomel electrode. These were then compared with the values calculated from the single potentials of the half-cells.

Kolthoff and Tomsicek (*loc. cit.*) measured the potentials between a quinhydrone electrode in 0·01N-hydrochloric acid plus 0·09N-potassium chloride (paH * = 2·075, and therefore $E_H = 576{\cdot}4$ mv.) against a ferri–ferro-cyanide (10 : 1) oxidation–reduction electrode. The value of E (total) was 102·0 mv. (quinhydrone positive), and therefore E_H of the complex cyanide half was 474·4 mv. The corresponding measurement with a ferro–ferri-cyanide (10 : 1) electrode was 208·8 mv.; $E_H = 357{\cdot}6$. Subtraction of the single potential of the saturated calomel electrode, 246 mv. at 25°, gives 228·4 and 111·6 mv. respectively for the potentials against calomel (negative).

Single potentials of the calomel electrode used were checked against quinhydrone in standard acetate at 18°. Mean values were (i) 186·3, (ii) 186·0 mv. (Calc.: 186·4). The potentials of smooth platinum electrodes in solutions with the above two ratios of the two cyanides against saturated calomel electrodes at 25° were 224 and 112 mv., respectively. Since the foregoing theoretical potentials are calculated as differences between different electrodes measured independently and probably with different technique, the agreement is satisfactory. A small initial potential E' is, however, indicated between a potassium ferricyanide solution I (positive) and saturated potassium chloride. As this opposes the liquid-junction potential $E_{I \rightarrow II}$ a small positive correction may be due, but it seems better not to introduce this, since it is probably temporary and less important than the uncertainties attributed to reversible hydrolysis with local production of a less mobile ion, $[Fe(OH)(CN)_5]^{3-}$.

Measurements on Potassium Sulphate.—Methods of determining transport numbers and their variation with concentration are well exemplified by potassium sulphate, and the diffusion potentials of this standard substance were therefore added to the data.

Conductivities over a wide range of concentrations are recorded in "International Critical Tables" and a few values at high dilutions are given by Hartley and Donaldson (*loc. cit.*), who also determined the transport numbers by the method of moving boundaries; ${}_0\lambda$ is 154·3, and this when combined with ${}_0l_+(K^+) = 73{\cdot}5$ gives ${}_0l_-(\frac{1}{2}SO_4^{--}) = 80{\cdot}8$ and $t_- = 0{\cdot}523$ (MacInnes, Longsworth, and Shedlovsky, *J. Amer. Chem. Soc.*, 1932, **54**, 2738), or if ${}_0l_+$ is taken as 74·8 and ${}_0l_-$ as 80·0, $t_- = 0{\cdot}517$ (Noyes and Falk, *ibid.*, 1911, **33**, 1436). The former value is in perfect agreement with that extrapolated from the experimental values of t_- (*a*) as obtained by the moving-boundary method, which were also compared with t_-, and (*b*) as calculated by the modified Onsager equation (3). In this calculation, ${}_0l_- = 0{\cdot}523$ and ${}_0\lambda = 154{\cdot}3$ have been used.

C, g.-equiv./l.	0·0	0·01	0·02	0·05	0·10
t, exptl.	0·523 (extrapol.)	0·517	0·515	0·513	0·511
$f(t_-, z)$	$-0{\cdot}215_5$	0·225		0·23	
t (Onsager)		0·513		0·50	
$f(t_-, z)$ (Onsager)		−0·23		−0·25	

Diffusion potentials are calculated from these data for the range 0·10—0·01 by means of the equation $E = f(t_-, z) \times 59$, in which the log of the concentration ratio is 1, and t_- refers to a mean concentration of 0·05. Thus, from (*a*), $E = 13{\cdot}6$ mv., and from (*b*), $E = 14{\cdot}75$ mv.

* Exponent of hydrogen-ion activity; this is essentially pH as usually defined (see Clark, "The Determination of Hydrogen Ions," 3rd edtn., pp. 201, 472).

(*c*) The experimental potentials over the ranges 0·01—0·001, 0·02—0·002, and 0·10—0·01 were 14—15 mv., agreeing with the values calculated on the assumption that the log of the concentration ratios can be used.

(*d*) The well-known relation between diffusion potentials and conductivity data will now be applied. In the equation

$$E = 59[(v - 2u)/2(u + v)] \log \gamma_1 C_1/\gamma_2 C_2$$

the velocities v and u will be taken as referring to a mean concentration of 0·05, the corresponding mobilities l_+ and l_- being derived from Kohlrausch's tables at 18°. It has been shown by Noyes and Falk (*loc. cit.*) that the relative values of l_+ and l_- at a given concentration and for a given valency type (still more, of course, for the same salt) do not vary much with temperature between 18° and 25°. Then $l_+ = 57{\cdot}9$ and $l_- = 46{\cdot}1$, both at $C = 0{\cdot}05$. The activities $a_\pm$ or γC refer to $C = 0{\cdot}10$ and 0·01, and $\log \gamma_1 C_1/\gamma_2 C_2 = 0{\cdot}91$. Therefore $E = 59 \times (-0{\cdot}335) \times 0{\cdot}91 = -18{\cdot}0$. If the activity coefficients of the ions, $\gamma_+ = 0{\cdot}887$ and $\gamma_- = 0{\cdot}662$, are multiplied by the mobilities l_0 at 25°, then $t_- = 0{\cdot}45$, $f(t_-, z) = -0{\cdot}325$, and since at 25° $\log \gamma_1 C_1/\gamma_2 C_2 = 0{\cdot}92$, $E = 59 \times (-0{\cdot}325) \times 0{\cdot}92 = -17{\cdot}6$.

(*e*) Activity coefficients are calculated from known ionic strengths, I, *i.e.*, for 0·10, 0·05, and 0·01N-potassium sulphate, by the Debye–Hückel equation ;

$$-\log f_\pm = 0{\cdot}505 z_+ z_- \sqrt{I} \text{ or } -\log f_i = 0{\cdot}505 z_i^2 \sqrt{I} \text{ at } 25°.$$

The same assumptions are made as in (*d*), *i.e.*, the individual coefficients of the ions $f_i \times {}_0f$ are used in the transport-number factor equation (4), and the mean activities in the log activity ratios. In the present case, $I = 0{\cdot}075$, $-\log f_+ = 0{\cdot}138$, $f_+ = 0{\cdot}728$, $-\log f_- = 0{\cdot}502$, $f_- = 0{\cdot}315$, $-\log {}_1f_\pm = 0{\cdot}124$, $-\log {}_1f_\pm = 0{\cdot}390$. Therefore $E = 59 \times (-0{\cdot}518) \times 0{\cdot}734 = -22{\cdot}4$.

It is thus evident that the introduction of activities into either (*d*) the conductivity equations or (*e*) the equations based on ionic strength, leads to high values of transport-number factors, which are only partly compensated for by the fact that log ratios of $a_\pm$ are lower than log ratios of C. The net result is that the diffusion potentials calculated are far higher than those observed. At concentrations higher than 0·05 and with the higher-valent complex cyanide ions, these disparities are still more marked. A few results are quoted below. Until, therefore, further mathematical analysis has revealed the causes of these discrepancies, it seems better in comparing results to use limiting mobilities and log concentrations throughout.

The transport numbers of bivalent cations in salts of type BA_2 have been extensively studied by Dole and his collaborators and found to vary considerably with concentration. The presence of an intermedate ion has been postulated in these cases. Bivalent anions have received less attention, but Noyes and Falk (*loc. cit.*) refer to them in these terms : "If the transport number of any tri-ionic salt is found constant through a considerable range of concentrations, it makes it somewhat probable, although it does not prove, that the intermediate ion is not present in considerable proportion in the solution." The present results, then, agree with the idea that the only ions present are K^+ and SO_4^{--}, and that the mobilities l_+ and l_- are either nearly constant or vary in nearly the same proportion, l_- or vF decreasing slightly faster than l_+ or uF. Suppose that the whole of the sulphate is present as an intermediate ion KSO_4^- ; then it can be shown that there must be a certain relation between its velocity v_1 and that of the bivalent ion v_2 in order that $f(t_-, z)$ should be nearly constant for the two kinds of ion or for any mixture. The relation is $v_1 = 3uv_2/(v_2 - 4u)$, *i.e.*, in the present case, $v_1 = 47{\cdot}5$. This, however, would reduce the transport number t_- from 0·523 to 0·393. Since t and $f(t_-, z)$ are found simultaneously and by independent methods to be nearly constant, it follows that there is only a minor proportion, if any, of an intermediate ion present in solutions up to 0·1N.

Measurements on Potassium Ferricyanide.—The conductivities of solutions of this salt at 25° have been determined by Schoch and Felsing (*J. Amer. Chem. Soc.*, 1916, **38**, 1928), and some values at low concentrations have been added by Hartley and Donaldson (*loc. cit.*), who give the highest value of $\lambda_0 = 174{\cdot}4$, which, when combined with l_+ for $K^+ = 73{\cdot}5$, gives $l_- = 101$, $t_- = 0{\cdot}578$, and $f(t_-, z) = 0{\cdot}23$. The values of t_- were determined by Hartley and Donaldson (*loc. cit.*), using the method of moving boundaries, and when extrapolated to $C = 0$ they are in perfect agreement with those based on limiting conductivities. They can also be calculated by the Onsager equation, the limiting values being used (fourth line) :

C	0·00	0·01	0·05	0·10
t_- (exptl.)	0·578	$0{\cdot}568_5$	0·560	$0{\cdot}557_5$
$f(t_-, z)$	0·23	$0{\cdot}24_4$	0·25	$0{\cdot}25_6$
t_- (Onsager)	(0·578)	$0{\cdot}561_5$	0·541	$0{\cdot}525_5$
$f(t_-, z)$	(0·23)	0·25	0·28	0·30
E (exptl., transport numbers)	13·6	14·4	14·8	15·1
E (Onsager)	(13·6)	14·8	16·5	17·7

When the calculated E values are compared with those obtained experimentally (marked * in Table I), they are seen to be in satisfactory agreement. Clearly, the introduction of the log activity ratio a (either from γC or from $f_\pm C$) would make the calculated values far too low. If, on the other hand, the transport-number factor is calculated from the activities assigned by the Debye–Hückel equation, then, on account of the low value of a tervalent ion, the factor soon approaches its limiting value of 1 (*i.e.*, when l_- and $v = 0$). Although the log activity ratio is also low, this does not compensate for the above, and the calculated E is too high, as already found in the case of potassium sulphate. Thus, for potassium ferricyanide at $C = 0{\cdot}05$, $\sqrt{I} = 0{\cdot}316$, $-\log f_+ = 0{\cdot}160$, $f_+ = 0{\cdot}692$, $-\log f_- = 1{\cdot}440$, $f_- = 0{\cdot}0363$; therefore $t_- = 0{\cdot}067$, and $f(t_-, z) = 0{\cdot}91$. At $C = 0{\cdot}10$ and 0·01, respectively, $-\log {}_1f_\pm$ and $-\log {}_2f_\pm$ are 0·679 and $0{\cdot}214_5$, hence $\log \gamma_1 C_1/\gamma_2 C_2 = 0{\cdot}545_5$. Therefore $E = 59 \times (0{\cdot}91) \times 0{\cdot}545_5 = 29{\cdot}3$. A modification of the Debye–Hückel equation has been suggested by Kielland (*J. Amer. Chem. Soc.*, 1937, **59**, 1675), *i.e.*,

$$\log f_i = -0{\cdot}5 z_i^2 \sqrt{I}/(1 + z_i \sqrt{I}) \text{ (inorganic ions)}$$

and

$$\log f_i = -0{\cdot}5 z_i^2 \sqrt{I}(1 + 2\sqrt{I}) \text{ (organic ions, including ferricyanide)}$$

Application of this to the same ferricyanide solution gives $-\log f_+ = 0{\cdot}120$, $f_+ = 0{\cdot}76$, $-\log f_- = 0{\cdot}875$, $f_- = 0{\cdot}1334$, $f(t_-, z) = 0{\cdot}92_3$, which does not greatly affect the value of E, provided that the log activity ratio remains the same. The use of activity equations in general leads to very low transport numbers of multivalent ions at moderate concentrations, and therefore to high diffusion potentials.

Conductivity data alone may be used to calculate the potentials with the aid of certain assumptions. The best agreement is obtained by assuming that l_+ of the potassium ion is the same as that in potassium chloride at the same normality. Then $l_- = \lambda - l_+$ is found to diminish with increasing concentration although not nearly so fast as the activity equations would indicate. Thus at $C = 0{\cdot}05$, $\lambda = 121{\cdot}4$, $l_+ = 65{\cdot}3$, $l_- = 56{\cdot}1$, $t_- = 0{\cdot}46_3$, and $f(t_-, z) = 0{\cdot}38_3$; at $C = 0{\cdot}10$, $\lambda = 113{\cdot}5$, and at $C = 0{\cdot}01$, $\lambda = 141{\cdot}7$; hence $\log \gamma_1 C_1/\gamma_2 C_2 = 0{\cdot}90_5$ and $E = 21{\cdot}0$.

TABLE I.

Solutions I, II	1·0, 0·1	0·4, 0·04	0·2, 0·02	0·1, 0·01	0·1, 0·002	0·1, 0·001
E, obs., mv.	20	20·1	19·0 *	17·2 *	30 (17·7)	35 (17·5)
or if (E) is reduced to log $C_I/C_{II} = 1$,						
Solutions I, II	0·05, 0·005	0·02, 0·002	0·02, 0·001	0·01, 0·002	0·01, 0·001	
E, mv. (as above)	15·1	15·4 *	19·9 (14·6)	10·5 (15·0)	14·0	

A line obtained by plotting E against $(C_I + C_{II})/2$ when $C_I/C_{II} = 10$ leads to $E = 12$—13 mv. at $C = 0$. The corresponding value from the extrapolated λ_0 and also ${}_0l_-$ is 13·5. At higher concentrations the observed values of E fall between those calculated from λ and those from t_-. From about $C = 0{\cdot}1$, E is 19—20 mv., and potentials then remain constant up to the highest concentrations investigated. A comparison at $C = 0{\cdot}10$ shows the extent of agreement between the different methods:

(*a*) From the experimental transport numbers, $t_- = 0{\cdot}56$, $f(t_-, z) = 0{\cdot}255$, $l_- = t_-\lambda = 63{\cdot}5$ ($\lambda = 113{\cdot}5$). (*b*) From the Onsager equation applied between $C = 0{\cdot}0$ and $0{\cdot}1$, $t_- = 0{\cdot}53$ and $l_- = 60{\cdot}5$. (*c*) From $E = 19{\cdot}0$ mv., $f(t_-, z) = 0{\cdot}32$, $t_- = 0{\cdot}52$ and $l_- = 58$. (*d*) From the conductivities alone, $t_- = 0{\cdot}44$, $l_- = 50{\cdot}0$. (*e*) At the higher mean concentration of 0·55, $E = 20{\cdot}0$, $f(t_-, z) = 0{\cdot}34$, $t_- = 0{\cdot}495$, $l_- = 0{\cdot}495 \times 98 = 49$.

In these calculations it is assumed that the only ions present are K^+ and $[Fe(CN)_6]^{3-}$. Although the values in (*b*) and (*c*) are in fair agreement, there is a discrepancy between (*a*) the transport number 0·56, which would require $f(t_-, z) = 0{\cdot}255$, and (*c*) the transport-number factor 0·32 from E. On the other hand, $f(t_-, z) = 0{\cdot}255$ would correspond to $E = 15{\cdot}0$, which is quite out of the question, since the potentials are very steady at these higher concentrations, and persist unchanged over a large range. The hypothesis of an intermediate ion, sometimes postulated, is attractive from several points of view. The strong interionic attraction of a multivalent ion appears to lead to the immobilisation of the cation in such an ion as $[KFe(CN)_6]^{2-}$. This hypothesis may be tested as follows. The mobility of $\frac{1}{2}[KFe(CN)_6]^{2-}$ may be taken provisionally to be the same as that of $\frac{1}{2}[Fe(CN)_5(NO)]^{2-} = 72{\cdot}5$ (Burrows and Turner, J., 1919, **115**, 1429). The mobility of $[Fe(CN)_6]^{3-}$ being 101, the fraction x of 1 g.-ion of ferricyanide is found which must be transformed into $1 - x$ of $[KFe(CN)_6]^{2-}$ in order to give the observed transport number $t_- = 0{\cdot}56$ at $C = 0{\cdot}10$. A special form of equation (2) is used, *viz.*,

$$-t_- = [v_3z_3x + v_2z_2(1 - x)]/\{v_3z_3x + v_2z_2(1 - x) + u[z_2 + (z_3 - z_2)x]\}$$

in which the denominator [see equation (2)] is the sum of the product of the velocity, the concentration, and the valency for each ion. From this, with $v_3 = 101$, $v_2 = 72{\cdot}5$, and $u = 73{\cdot}5$, we have $x = 0{\cdot}65$.

The transport-number factor $f(t_-, z)$ for a salt giving several kinds of anions can be obtained from the equation

$$f(t_-, z) = \frac{1}{z_3} \cdot \frac{v_3z_3x}{D} + \frac{1}{z_2}\frac{v_2z_2(1 - x)}{D} - \frac{u[z_2 + (z_3 - z_2)x]}{D}$$

where D is the above common denominator. Applying this to the present case, we have $f(t_-, z) = v_3x/(D) + v_2(1 - x)/D - u(2 + x)/D = -104/442{\cdot}7_5 = -0{\cdot}23_5$. This is lower than any of the values calculated from (*a*) transport numbers, (*b*) conductivities, or (*c*) diffusion potentials, on the assumption that the only anion present is $[Fe(CN_6)]^{3-}$. Also the value of the equivalent conductivity, λ, calculated from the mobilities of the ions (including the intermediate ion) given above would be $442{\cdot}75/3 = 147{\cdot}5$, as against the observed 113·5. On the other hand, if x is calculated from $3\lambda = 340{\cdot}5$, *i.e.*, $\lambda = \Sigma l_- + \Sigma l_+$, then $x = 0{\cdot}21$. The corresponding value of t_- is 0·52 and the factor is 0·248,* again below any experimental value. In fact, no value which can be assigned to the mobility of the intermediate ion is in agreement simultaneously with the experimental results (*a*), (*b*), and (*c*) above.

Measurements on Potassium Ferrocyanide.—The conductivities of this salt at 25° have been determined by Noyes and Johnston (*J. Amer. Chem. Soc.*, 1909, **31**, 987) and by Schoch and Felsing (*loc. cit.*). The extrapolated value of λ_0 is 185·5; therefore l_0 for $\frac{1}{4}[Fe(CN)_6]^{4-}$ is 112. The ratio of this to l_0 for $\frac{1}{3}[Fe(CN)_6]^{3-}$ is 1·11, instead of 1·33 by the valency rule. The values of λ diminish with concentration more rapidly than those of the ferricyanide. Assuming, as before, that l_+ for K^+ has the value which is found in a solution of potassium chloride having the same concentration, the values of t_- and l_- are found to diminish rapidly, as shown in Table II. In this table the Onsager equation has also been used

TABLE II.

Transport numbers of potassium ferrocyanide from conductivity values.

C, g.-equiv./l.	0·00	0·002	0·005	0·010	0·020	0·050	0·100	0·200	0·500	1·00
λ	185·5	160·1	146·9	$135{\cdot}3_5$	123·3	108·3	98·2	$89{\cdot}7_5$	81·0	77·2
α	1·00	$0{\cdot}86_5$	0·794	0·732	0·667	0·586	0·530	0·485	0·438	0·417
l_-	112	87·9	75·9	69·7	55·0	43·0	34·7	$28{\cdot}7_5$	23·1	20·2
t_-	0·603	0·555	0·515	0·485	0·445	0·396	0·353			
$f(t_-, z)$	0·245	0·315	0·355	0·385	0·443	0·503	0·555			
t_- (from Onsager's equation)	0·5470	0·524								
$f(t_-, z)$,, ,, ,,	0·3160	0·345								

to give a value of t_-. Thus $dt_+/dc = 0{\cdot}25$, and if $t_- = 0{\cdot}603$ at $C = 0{\cdot}0$, then at $C = 0{\cdot}05$, $\Delta t_- = -0{\cdot}056_5$ and $t_- = 0{\cdot}54_6$; t_- derived from the diffusion potential is 0·53. In general, values of t_- derived from E agree well with those from the Onsager equation, even up to concentrations above 0·1, at which this equation would not be expected to apply. Thus at $C \sim 0{\cdot}1$, t_- (from E) = 0·516 and t_- (from Onsager's equation) = $0{\cdot}523_5$; whereas at $C \sim 0{\cdot}275$, $t_- = 0{\cdot}447$ in both cases.

By plotting E against $(C_I + C_{II})/2$, a linear graph is obtained, which on extrapolation gives $E = 14{\cdot}5$ at $C = 0$.

The production of one or more intermediate ions from the ferrocyanide is rendered more probable by the higher ionic charge, and the data were therefore examined by methods somewhat similar to those used with the ferricyanide. In potassium ferrocyanide, the presence of osmotically inactive molecular species is shown by the osmotic (freezing-point) activity coefficient $i = 3{\cdot}57$, and a high proportion of electrically inactive molecules is shown by the conductimetrically determined $i = 3{\cdot}37$; both values of i relate to $C = 0{\cdot}05$ g.-equiv./l. (Noyes and Johnston, *loc. cit.*). The diminution in activity may, however, also be due to the formation of intermediate ions. If the mobilities of all ions are assumed to be the limiting values ${}_0l$, then it is clear that *all* the anion must be present as $[KFe(CN)_6]^{3-}$ and $[K_2Fe(CN)_6]^{2-}$. The proportion of tervalent ion x can be calculated which will give the observed value of λ, and then the corresponding trans-

* In these calculations the preceding equation for $f(t_-, z)$ is used, and $D = 340{\cdot}5$.

TABLE III.

Diffusion potentials of potassium ferrocyanide.

C_I, C_{II}, and mean.	log $(aC_I)/(aC_{II})$.	E_d, calc. from λ.*	E, obs.†	C.	E, calc. by Onsager's equatn.
0·5, 0·05; 0·275	$0{\cdot}87_4$	31·5	26·0		
0·4, 0·04; 0·22	0·87	31·0	24·3		
0·2, 0·02; 0·11	0·86	28·5	21·5	0·10	20·4
0·1, 0·01; 0·055	$0{\cdot}86_1$	25·9	20·2	0·05	18·7
0·1, 0·005; 0·0525	$1{\cdot}12_5$	33·5	26 (20)		
0·1, 0·002; 0·051	$1{\cdot}48_7$	44·2	32·0 (18·8)		
0·1, 0·001; 0·0505	$1{\cdot}76_1$	52·2	38·0 (19·0)		
0·05, 0·005; 0·0275	$0{\cdot}86_8$	23·5	16·0		
0·02, 0·002; 0·011	$0{\cdot}88_7$	20·6	16·0	0·01	16·4
0·02, 0·001; 0·0105	$1{\cdot}16_1$	26·6	22·5 (17·3)		
0·01, 0·002; 0·006	$0{\cdot}62_6$	13·1	10·6 (15·2)		
0·01, 0·001; 0·0055	$0{\cdot}90_0$	18·1	16·0	0·00	(14·5)

* *I.e.*, $f(t_-, z) \times 59 \times \log(aC)$ ratio.
† Values in parentheses are those of E reduced to $\log C_I/C_{II} = 1$.

port number can be compared with that calculated from E. Experimental quantities at $C = 0{\cdot}05$ are: $\lambda = 108{\cdot}3$, $E = 20$, therefore $f(t_-, z) = -0{\cdot}34$ and $t_- = 0{\cdot}53$. From the equation $\lambda = \Sigma l_- + \Sigma l_+$, $x = 0{\cdot}61$. In this calculation l_- of $\frac{1}{4}[KFe(CN)_6]^{3-}$ is taken as 101, that of $\frac{1}{4}[KFe(CN)_6]^{4-}$ as 72·5. The above value of x leads to an activity coefficient $i = 3 + x = 3{\cdot}61$. This is in agreement with the coefficient determined by cryoscopic methods (above). Now, by the equations already illustrated in the case of potassium ferricyanide, transport numbers and their factors can be calculated which correspond to the intermediate ions. Thus, from $x = 0{\cdot}61$, $t_- = 0{\cdot}56$ and $f(t_-, z) = 0{\cdot}235$. This is far lower than the value corresponding to the diffusion potential at $C = 0{\cdot}05$. Although mobilities can be assigned to the intermediate ions which would reproduce the experimental transport-number factor, they would then not reproduce the experimental values of ${}_0\lambda$, t_-, and i. Hence, the theory of intermediate ions fails to overcome the difficulties in interpreting the present results, together with previous data, for potassium ferrocyanide.

Comparison of Potassium Ferri- and Ferro-cyanide.—The limiting values of the quantities expressed by the symbols are in close agreement when calculated (1) from ${}_0\lambda$ and (2) from E, and can therefore be represented by single sets of figures, which are deduced in the order shown by the arrows in the two cases. Thus, (1): from ${}_0\lambda$, by subtracting ${}_0l_+$, ${}_0l_-$ is obtained, and hence t_-, and by the use of equation (5) or (6), $f(t_-, z)$; also, by the use of (4), E is found. Next, (2): from E, $f(t_-, z)$ and t_- are obtained, and then ${}_0l_-$ by the use of ${}_0\lambda$.

		${}_0\lambda$.	${}_0l_-$.	${}_0t_-$.	$f(t_-, z)$.	E.	
$K_4Fe(CN)_6$	(1) →	185·5	112	0·604	0·245	14·5	← (2)
$K_3Fe(CN)_6$	(1) →	174·4	101	0·578	0·230	13·5	← (2)

In the solutions approaching limiting dilution, $[Fe(CN)_6]^{4-}$ is the more mobile ion, as theory requires, and it is confirmed by diffusion potentials that at low concentrations the ratio of ${}_0l_4$ to ${}_0l_3$ = 1·11.

The fact that the potentials of the ferro- and ferri-cyanides only differ by a millivolt at a point obtained by extrapolation suggests that these potentials are equal at $C = 0$. (If Schoch and Felsing's value of $\lambda_0 = 168$ for the ferricyanide is accepted, $t_- = 0{\cdot}56$, and $f(t_-, z) = 0{\cdot}25$; *i.e.*, it is practically identical with that of the ferrocyanide.)

If the potentials of the two salts are equal, and $\log C_I/C_{II}$ is equal to 1 in each case, then $f(t_-, z)$ is also equal for the ferri- and the ferro-cyanide. If we represent this value by $-a$, then by transposition of equation (6) we have

$$\frac{u}{v_4} + 1 = \frac{1}{{}_4t_-} = \frac{5}{4}\left(\frac{1}{1-a}\right) \text{ and } \frac{u}{v_3} + 1 = \frac{1}{{}_3t_-} = \frac{4}{3}\left(\frac{1}{1-a}\right)$$

Therefore, $v_4/v_3 = (4 + 12a)/(3 + 12a)$. If $E = 14{\cdot}0$ mv., then $a = 0{\cdot}2375$ and $v_4/v_3 = 1{\cdot}17$.

The graphs of E against C diverge as C increases, the slopes are very gradual, nearly parallel, and separated by about 3 mv., that of the ferrocyanide being the upper. In the following table, the transport numbers and mobilities of the two ions are compared at $C = 0{\cdot}05$, 0·10, and 0·20.

The mobilities of ferro- and ferri-cyanide ions at higher concentrations.

	Potassium ferricyanide.			Potassium ferrocyanide.		
C, g.-equiv./l.	0·05	0·10	0·20	0·05	0·10	0·20
t_-(Onsager)	0·541	0·526	0·504	0·546	0·524	0·490
E, mv. (from graph)	17·5	19·0	20·0	19·0	21·5	24·0
$f(t_-, z)$	−0·297	0·322	0·340	−0·322	0·365	0·407
t_-(from E)	0·525	0·509	0·495	0·542	0·510	0·475

The small but steady differences between the values of E for the two salts at the same concentration, when introduced into equation (6), evidently lead to an approximate equality in t_-, which becomes almost complete at $C = 0{\cdot}10$, whereas equality is nearly attained from $C = 0{\cdot}05$ according to Onsager's equation.

I have much pleasure in expressing thanks for the interest of colleagues and the facilities of the Chemistry Department of this College, and especially for the loan of a pH meter by Imperial Chemical Industries Ltd., and also for other apparatus acquired by means of a former grant from the Chemical Society.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, March 24th*, 1944.]

166. *The Preparation of Some Stilbene Derivatives. Part III.*

By H. J. Barber and R. Slack.

Some alkylstilbene diamidines, which are higher homologues of the therapeutically active 4 : 4′-diamidinostilbene ("Stilbamidine"), have been prepared. The preparation of the required intermediates has involved a study of various synthetic methods in the stilbene series.

The fact that diamidines of the type $NH_2{\cdot}C(:NH){\cdot}C_6H_4{\cdot}CR{:}CR'{\cdot}C_6H_4{\cdot}C(:NH){\cdot}NH_2$, especially (I; R = R′ = H) and (II; R = R′ = CH_3), have shown trypanocidal activity (Kirk and Sati, *Ann. Trop. Med. Parasitol.*, 1940, **34**, 83; Fulton and Yorke, *ibid.*, 1942, **36**, 131; Napier *et al.*, *Indian Med. Gaz.*, 1942, **77**, 321), has prompted further investigation of derivatives, *e.g.* (III; R = H, R′ = CH_3), (IV; R = H, R′ = C_2H_5), and (V; R = R′ = C_2H_5).

The preparation of (III) and (IV) presented little difficulty, for it was found that the most convenient method of preparation of the monosubstituted stilbenes was from the parent deoxybenzoin, the method used by Dodds *et al.* (*Proc. Roy. Soc.*, 1939, *B*, **127**, 140) for the stilboestrol series. This method had the disadvantage that the carbinols $CH_2R{\cdot}\overset{|}{C}(OH){\cdot}\overset{|}{C}H{\cdot}CH_2R'$ could lead to a mixture of structural isomerides as well as the normal *cis*- and *trans*-stilbenes. This was corroborated by experiments carried out in these laboratories and by Walton and Brownlee (*Nature*, 1943, **151**, 305). This method also failed with mononuclear hydrogenated deoxybenzoins (Ruggli and Businger, *Helv. Chim. Acta*, 1942, **24**, 112).

In seeking an unambiguous route to (V), that of Barber, Slack, and Woolman (J., 1943, 99) for the corresponding αβ-dimethylstilbene (II) was first examined. Bromination of either *meso*- or racemic γδ-diphenyl-*n*-hexane in acetic acid gave a *hexabromo*-compound which was not orientated. From the *meso*-form a solid *dibromo*-compound was also isolated but the racemic hydrocarbon yielded a non-distillable gum. The solid dibromo-compound was converted by way of the nitrile and iminoether into the diamidine, a sequence which indicates probable 4 : 4′-disubstitution. These products are therefore regarded as 4 : 4′-dibromo-, 4 : 4′-*dicyano*-, and 4 : 4′-*diamidino*-γδ-*diphenyl*-n-*hexanes*.

Other methods, *e.g.*, the decomposition of thiopropiophenone (Linnell and Sharma, *Quart. J. Pharm.*, 1939, **12**, 263) and the thermal decomposition of azines (Curtius and Jay, *J. pr. Chem.*, 1889, **39**, 45; Linnell and Sharma, *loc. cit.*; Barber and Slack, *J. Amer. Chem. Soc.*, 1943, **65**, 1776), gave no promise of success. Some experiments were, however, carried out on the decomposition of substituted dibromobenzaldazines (VI; R = R′ = CH_3 or C_2H_5) by cuprous cyanide in boiling quinoline, in the hope that loss of nitrogen and cyanation would occur simultaneously. The only product isolated, after treatment with mineral acid, was 4-cyanopropiophenone.

(VI.) $C_6H_4Br{\cdot}CR{:}N{\cdot}N{:}CR'{\cdot}C_6H_4Br$ $C_6H_5{\cdot}CHEt{\cdot}SO_3H$ (VII.)

Model experiments indicated that α-phenylpropyl chloride would not give the sulphonic acid (VII), so Ruggli's method (*Helv. Chim. Acta*, 1931, **14**, 541) was not practicable. Similarly, the direct introduction of the cyano-group by trichloroacetonitrile (Houben and Fischer, *Ber.*, 1933, **66**, 339) failed in the case of stilbene, though a very unstable imine hydrochloride of the type $[CCl_3{\cdot}C(:NH){\cdot}C_6H_4{\cdot}CH{:}]_2$ was formed. Experiments in other directions included the following scheme :

$C_6H_4Br{\cdot}CH_2{\cdot}CN \longrightarrow C_6H_4Br{\cdot}CHAc{\cdot}CN$ (VIII.) $\longrightarrow C_6H_4Br{\cdot}CAc(CN){\cdot}CAc(CN){\cdot}C_6H_4Br$ (IX.)

$\longrightarrow C_6H_4Br{\cdot}CHAc{\cdot}CHAc{\cdot}C_6H_4Br$ (X.) $\longrightarrow C_6H_4Br{\cdot}CAcBr{\cdot}CAcBr{\cdot}C_6H_4Br$ (XI.

p-Bromophenylacetonitrile reacted smoothly with ethyl acetate in the presence of sodium ethoxide to give *acetyl*-p-*bromophenylacetonitrile* (VIII). Oxidation by perhydrol in glacial acid gave 3 : 4-*dicyano*-3 : 4-*di*-(p-*bromophenyl*)-2 : 5-*diketohexane* (IX), which we failed to hydrolyse.

During this work, Vargha and Kovács (*Ber.*, 1942, **75**, 794) published a synthesis of the intermediate required, *viz.*, 4 : 4′-dibromo-αβ-diethylstilbene, by a modification of a method due to Staudinger (*Ber.*, 1916, **49**, 1942):

$C_6H_4R{\cdot}CEt{:}N{\cdot}NH_2 \longrightarrow C_6H_4R{\cdot}CEt{:}N_2 \longrightarrow C_6H_4R{\cdot}CEt{-}\underset{\diagdown\,\diagup}{SO_2}{-}CEt{\cdot}C_6H_4R \longrightarrow C_6H_4R{\cdot}CEt{:}CEt{\cdot}C_6H_4R$

(XIV.) (XV.) (XVI.) (XVII.)

4-*Cyanopropiophenonehydrazone* (XIV; R = CN), when submitted to the above series of reactions, gave a product, presumably 4 : 4′-*dicyano*-αβ-*diethylstilbene* (XVII; R = CN). With the aim of confirming this structure, a parallel synthesis of the well-characterised 4 : 4′-dibromo-αβ-dimethylstilbene (Barber, Slack, and Woolman, *loc. cit.*) from 4-*bromoacetophenonehydrazone* was performed, but the final product contained sulphur (cf. Linnell and Sharma, *loc. cit.*). Similarly 4-cyanoacetophenone failed to give 4 : 4′-dicyano-αβ-dimethylstilbene, so confirmation was still lacking.

The marked influence of R and R′ in the aryl ketones, $C_6H_4R{\cdot}COR'$, on their behaviour in this series of reactions is noteworthy, especially since it is shown that inaccessible anhydrous hydrazine is not always necessary to obtain hydrazones (see table below).

R.	R′.	Product from hydrazine hydrate.	Product from Vargha and Kovács's reactions.
CN	H	Azine	—
Br	CH_3	Hydrazone	No stilbene
Br	C_2H_5	Azine	Stilbene (V. and K., *loc. cit.*)
CN	CH_3	Hydrazone	No stilbene
CN	C_2H_5	Hydrazone	Stilbene

Finally, to settle the structure of our product (XVII; R = CN), we returned to the route from 4 : 4′-dibromodeoxybenzoin with two main aims, *viz.*, the isolation of specimens of *cis*- and *trans*-4 : 4′-dibromo-αβ-dimethylstilbene identical with those obtained from βγ-diphenyl-*n*-butane, and the isolation of a dibromodiethylstilbene, identical with that of Vargha and Kovács (*loc. cit.*), which could be converted into the same dicyanodiethylstilbene as that obtained from *p*-cyanopropiophenonehydrazone.

$$\underset{\text{(XVIII.)}}{C_6H_4Br\cdot CO\cdot CH_2\cdot C_6H_4Br} \longrightarrow \underset{\text{(XIX.)}}{C_6H_4Br\cdot CO\cdot CHR\cdot C_6H_4Br} \longrightarrow \underset{\text{(XX.)}}{C_6H_4Br\cdot CR'(OH)\cdot CHR\cdot C_6H_4Br} \longrightarrow C_6H_4Br\cdot CR'{:}CR\cdot C_6H_4Br \quad \text{(XXI.)}$$

An improved method for preparing 4 : 4′-dibromodeoxybenzoin, hitherto made by condensation of *p*-bromophenacetyl chloride with bromobenzene, was found in the addition of the elements of water to 4 : 4′-*dibromotolan* which was readily available from 4 : 4′ : α : β-tetrabromo-αβ-diphenylethane.

4 : 4′-Dibromodeoxybenzoin (XVIII) reacted normally with methyl- and with ethyl-magnesium halides to form 1 : 2-*di*-(p-*bromophenyl*)-n-*propan*-2-*ol* (XX; R = H, R′ = Me) and the corresponding n-*butan*-2-*ol* (XX; R = H, R′ = Et), respectively; these were converted by anhydrous potassium hydrogen sulphate into the corresponding 4 : 4′-*dibromo*-α-*methyl*- and -α-*ethyl*-*stilbenes* (XXI; R = H) and these, in turn, were converted by way of the *nitriles* into 4 : 4′-*diamidino*-α-*methyl*- and -α-*ethyl*-*stilbenes*. *cis*- and *trans*-Forms were obtained in both series but could usually be separated by fractional crystallisation.

4 : 4′-*Dibromo*-α-*methyl*- and -α-*ethyl*-*deoxybenzoin* (XIX; R = Me or Et) were obtained from 4 : 4′-dibromodeoxybenzoin by means of methyl and ethyl iodide, respectively, and 4 : 4′-*dibromo*-α-*benzyldeoxybenzoin* by means of benzyl chloride. The first two compounds reacted normally with methyl- and ethyl-magnesium bromide, respectively. Some difficulty was experienced in dehydrating smoothly the resulting 2 : 3-*di*-(p-*bromophenyl*)-n-*butan*-2-*ol* and 3 : 4-*di*-(p-*bromophenyl*)-n-*hexan*-3-*ol*, (XX; R = R′ = Me) and (XX; R = R′ = Et). Phosphorus tribromide was useless, but acetic anhydride–acetyl chloride or anhydrous potassium hydrogen sulphate was better, and from the resulting oils 4 : 4′-dibromo-αβ-dimethyl- and -αβ-diethyl-stilbenes (XXI; R = R′ = Me or Et) were finally isolated in crystalline form. Treatment of the diethyl compound with bromine gave 4 : 4′ : γ : δ-*tetrabromo*-γδ-*diphenyl*-n-*hexane*.

In this series of experiments, the possibility of the type of rearrangement recorded by Földi (*Ber.*, 1941, 74, 930), *e.g.*

$$CH_3\cdot O\cdot C_6H_4\cdot CHCl\cdot CO\cdot C_6H_4\cdot O\cdot CH_3 \xrightarrow{2\,C_2H_5MgX} CH(C_6H_4\cdot O\cdot CH_3)_2\cdot CEt_2\cdot OH$$

was not overlooked but unsymmetrically substituted ethylenes were not found in the dehydration products.

Experimental.

Bromination of γδ-*Diphenyl*-n-*hexane*.—*Solid hydrocarbon*. (*a*) The hydrocarbon (2·3 g.), acetic acid (21 c.c.), and bromine (9·0 g.) were heated under reflux for 4 hours. After cooling, a white crystalline solid (2·8 g.), m. p. 150—190°, separated. Division into two components by washing with ether, followed by separate fractional crystallisation from acetic acid, gave the *dibromo*- (0·4 g.), m. p. 170—172° (Found : Br, 40·2. $C_{18}H_{20}Br_2$ requires Br, 40·4%), and the *hexabromo*-compound, m. p. 215° (decomp.) (Found : Br, 67·1. $C_{18}H_{16}Br_6$ requires Br, 67·2%).

(*b*) The hydrocarbon (10 g.), bromine (33·6 g.), and chloroform (50 c.c.) were heated under reflux for 4 hours, and the solvent then removed by distillation. The solid which separated recrystallised from glacial acetic acid to give the above dibromo-compound (10·2 g., 64·5%).

Liquid hydrocarbon. The hydrocarbon (10 g.), bromine (33·6 g.), and acetic acid (87 c.c.) were heated under reflux until the colour of the bromine had disappeared. When the hot liquors were seeded with a specimen of the hexabromo-compound, this separated in a pure form (4·1 g.), m. p. 215° (decomp.).

4 : 4′-*Dicyano*-γδ-*diphenyl*-n-*hexane*.—Dibromo-γδ-diphenyl-*n*-hexane (10 g.) and cuprous cyanide (11·3 g.) were added slowly to boiling quinoline (100 c.c.). The reaction mixture was worked up with hydrochloric acid, and the crude product recrystallised from glacial acetic acid, giving the *dicyano*-compound (4 g.), m. p. 193° (Found : N, 9·74. $C_{28}H_{20}N_2$ requires N, 9·75%).

4 : 4′-*Diamidino*-γδ-*diphenyl*-n-*hexane*.—The nitrile (2·0 g.), in chloroform solution, was converted into the iminoether hydrochloride in the usual manner (8 days). The free iminoether base, liberated from the hydrochloride by treatment with ice and sodium hydroxide solution, gave the required *amidine isethionate* on being heated with ammonium isethionate in aqueous-alcoholic solution (Found : N, 9·56. $C_{32}H_{32}O_4N_4S_2$ requires N, 9·76%).

α-*Acetyl*-p-*bromobenzyl Cyanide* (VIII).—*p*-Bromobenzyl cyanide (25 g.) was treated with sodium (8·5 g.) in alcohol (85 c.c.). Ethyl acetate (35 c.c.) was then added all at once, and the mixture heated under reflux for 4 hours. It was then poured into water, filtered, extracted once with ether, and acidified; a red oil, which rapidly solidified, was obtained. Crystallisation from benzene gave the *acetyl* derivative (15 g.) as white, rectangular plates, m. p. 134° (Found : N, 5·9. $C_{10}H_8ONBr$ requires N, 5·9%).

3 : 4-*Dicyano*-3 : 4-*di*-(p-*bromophenyl*)-2 : 5-*diketo*-n-*hexane* (IX).—The acetyl derivative (1·0 g.) was dissolved in acetic acid (5·0 c.c.), treated with hydrogen peroxide (1 c.c., 30-vol.), and kept at 100°, the product separating from the hot solution. After cooling, a total yield of 0·6 g. was obtained, and recrystallisation from acetic acid gave the pure *compound*, m. p. 225° (Found : N, 5·9. $C_{20}H_{14}O_2N_2Br_2$ requires N, 5·9%).

p-*Cyanopropiophenonehydrazone* (XIV; R = CN).—*p*-Cyanopropiophenone (5 g.) (B.P. 488,642) was heated with hydrazine hydrate (10·0 c.c., 50% w/w solution) and alcohol (10 c.c.) for 2 hours. The *hydrazone* was isolated by precipitation with water; it was then dissolved in ether, dried (sodium sulphate), and precipitated by addition of ligroin; the unstable product (4 g.), m. p. 80—81°, had to be analysed immediately (Found : N, 23·9. $C_{16}H_{11}N_3$ requires N, 24·2%).

4 : 4′-*Dicyano*-αβ-*diethylstilbene*.—The hydrazone from 5 g. of ketone was shaken in a closed vessel with yellow mercuric oxide (8 g.) and ligroin (50 c.c.) at room temperature for 4 hours. The cherry-red solution obtained by filtration was treated with a rapid stream of sulphur dioxide at 0° to give 1·2 g. of a yellow amorphous solid; when heated to 120°, this lost sulphur dioxide, leaving a gummy mass which on trituration with ether gave crude 4 : 4′-*dicyano*-αβ-*diethylstilbene* (0·5 g.). Crystallisation from alcohol gave white needles, m. p. 216° (Found : C, 83·5; H, 6·2; N, 9·8. $C_{28}H_{18}N_2$ requires C, 84·0; H, 6·3; N, 9·8%).

p-*Bromoacetophenonehydrazone*.—*p*-Bromoacetophenone (20 g.), hydrazine hydrate (10 g., 50% w/w), and alcohol

(100 c.c.) were heated under reflux for 3 hours, then poured into water; the *hydrazone*, m. p. 164°, separated (Found: N, 13·6. $C_8H_9N_3Br$ requires N, 13·1%). In view of the known instability of hydrazones of this type, further purification was inadvisable.

p-*Cyanoacetophenonehydrazone*, m. p. 73—74°, was similarly prepared (Found: N, 26·5. $C_9H_9N_3$ requires N, 26·4%).

4 : 4′-*Diamidino-αβ-diethylstilbene*.—The nitrile (1·0 g.) was converted into the iminoether hydrochloride (5 days) in chloroform (10 c.c.) and alcohol (1·0 c.c.). The iminoether base, obtained as a white solid, m. p. 98—100°, gave the required *amidine dihydrochloride* (0·6 g.) when heated in aqueous alcohol with ammonium chloride (Found: N, 13·3; Cl, 16·46. $C_{20}H_{24}ON_2$ requires N, 13·1; Cl, 16·5%).

4 : 4′-*Dibromotolan*.—4 : 4′ : α : β-Tetrabromo-αβ-diphenylethane (10 g.) was treated with a solution of sodium (9·2 g.) in alcohol (150 c.c.), the mixture heated under reflux for ½ hour (2—3 hours for larger preparations), and poured into water. The crude tolan, m. p. 170—180°, crystallised from chloroform or dioxan, gave 5 g. of *dibromo*-compound, m. p. 182—184° (Found: Br, 47·6. $C_{14}H_8Br_2$ requires Br, 47·6%).

4 : 4′-*Dibromodeoxybenzoin* (XVIII).—4 : 4′-Dibromotolan (40 g.) was heated with concentrated sulphuric acid (200 c.c.) and acetic acid (600 c.c.) to complete solution. Vigorous mechanical agitation was essential. After cooling, the whole was diluted with water, the solid collected, dried, and recrystallised from glacial acetic acid, giving 35 g. of the *deoxybenzoin*, m. p. 137° (Found: Br, 45·1. $C_{14}H_{10}OBr_2$ requires Br, 45·2%). The *semicarbazone* had m. p. 210—212° (Found: N, 10·2. $C_{15}H_{13}ON_3Br_2$ requires N, 10·2%).

1 : 2-*Di*-(p-*bromophenyl*)-n-*propan*-2-*ol* (XX; R = H, R′ = Me).—4 : 4′-Dibromodeoxybenzoin (40 g.) was added in small portions to the Grignard solution prepared from magnesium (8·2 g.), methyl iodide (52 g.), and ether (250 c.c.) maintained at 0°. After standing overnight at room temperature, the reaction mixture was worked up with ammonium chloride. Distillation of the product, b. p. 195—200°/0·5 mm., gave the *carbinol* (32 g.) as a white solid, m. p. 62° (Found: Br, 43·1. $C_{14}H_{10}OBr_2$ requires Br, 43·3%).

4 : 4′-*Dibromo-α-methylstilbene* (XXI; R = H, R′ = Me).—The above carbinol (5 g.) was heated with anhydrous potassium hydrogen sulphate (2 g.) at 180—190° for 15 minutes. The water formed was removed in a vacuum. Extraction of the reaction mixture with boiling benzene gave 3 g. of the trans-*stilbene*, m. p. 136—137° (Found: Br, 45·4. $C_{15}H_{12}Br_2$ requires Br, 45·5%). From the mother-liquors the cis-*compound* (prisms from methyl alcohol), m. p. 73·5°, was obtained (Found: Br, 45·6%).

4 : 4′-*Dicyano-α-methylstilbene*.—4 : 4′-Dibromo-α-methylstilbene (4·8 g.), cuprous cyanide (2·7 g.), and quinoline (15 c.c.) were heated under reflux for 20 minutes. After being worked up in the usual manner and sublimed in a vacuum, 3·0 g. of crude product were obtained. Recrystallisation from glacial acetic acid gave the *dicyano*-compound (2·6 g.), m. p. 153—155° (Found: N, 11·2. $C_{17}H_{12}N_2$ requires N, 11·5%).

4 : 4′-*Diamidino-α-methylstilbene*.—The dicyano-compound (8 g.) was converted into the iminoether hydrochloride (2 days); this gave the corresponding *amidine dihydrochloride* (6 g.) on being heated for 6 hours at 45° with saturated alcoholic ammonia. It separated from dilute hydrochloric acid in pale yellow crystals (Found: N, 15·0; Cl, 19·2. $C_{17}H_{18}N_4,2HCl,H_2O$ requires N, 15·1; Cl, 19·2%).

1 : 2-*Di*-(p-*bromophenyl*)-n-*butan*-2-*ol* (XX; R = H, R′ = Et).—4 : 4′-Dibromodeoxybenzoin (50 g.) was added in portions to the cooled Grignard solution from magnesium (10·2 g.), ethyl bromide (46 g.), and ether (500 c.c.), and after being heated under reflux for 2 hours the reaction mixture was worked up with dilute sulphuric acid. Removal of the ether gave the product as an oil (54 g.) which was not distilled, as this causes partial dehydration.

4 : 4′-*Dibromo-α-ethylstilbene* (XXI; R = H, R′ = Et).—The foregoing oil (54 g.) was intimately mixed with anhydrous potassium hydrogen sulphate (24 g.), heated under 16 mm. at 190° for one hour, and the residue distilled; b. p. 190—195°/0·5 mm. 4 : 4′-Dibromostilbene (2·0 g.), m. p. 202°, was separated, and the mixture of cis- and trans-*stilbenes* redistilled; b. p. 183—185°/0·3 mm. (Found: Br, 43·7. $C_{16}H_{14}Br_2$ requires Br, 43·7%).

4 : 4′-*Dicyano-α-ethylstilbene*.—The mixed isomerides (20 g.) and cuprous cyanide (10·8 g.) were boiled in quinoline (40 c.c.) for 30 minutes. The oil which separated on pouring the reaction mixture into concentrated hydrochloric acid was extracted with chloroform, the extract washed with water, dried (sodium sulphate), and the solvent was removed; the residue distilled as a yellow oil (11 g.), b. p. 198—200°/0·4 mm. Treatment of the oil with glacial acetic acid gave 3 g. of the trans-*nitrile*, which, recrystallised from ethanol, had m. p. 126—128° (Found: N, 10·9. $C_8H_{14}N_2$ requires N, 10·9%). The acetic acid liquors gave 5 g. of mixed isomerides from which 2·6 g. of the pure cis-*nitrile*, m. p. 90—92°, were isolated by fractional crystallisation from glacial acetic acid and recrystallisation from ligroin (b. p. 60—80°) (Found: N, 10·9%).

trans-4 : 4′-*Diamidino-α-ethylstilbene*.—The nitrile was converted into the corresponding iminoether base in the usual manner (5 days). Treatment with ammonium chloride in aqueous alcohol gave the *amidine hydrochloride* (Found: N, 14·6; Cl, 18·5. $C_{20}H_{24}N_4,2HCl,H_2O$ requires N, 14·5; Cl, 18·5%).

4 : 4′-*Dibromo-α-methyldeoxybenzoin* (XIX; R = Me).—4 : 4′-Dibromodeoxybenzoin (52 g.) was dissolved in alcohol (75 c.c.) containing sodium (4 g.). Methyl iodide (50 g.) was added all at once. When the vigorous reaction had subsided, the mixture was heated under reflux until neutral to litmus, water was added, and the alcohol removed by distillation. Extraction of the aqueous suspension with benzene, followed by removal of the solvent and crystallisation of the residue from methanol, gave the required *product*, m. p. 69—70° (40 g.) (Found: Br, 43·4. $C_{15}H_{12}OBr_2$ requires Br, 43·5%).

2 : 3-*Di*-(p-*bromophenyl*)-n-*butan*-2-*ol* (XX; R = R′ = Me).—4 : 4′-Dibromo-α-methyldeoxybenzoin (32 g.) was added to the Grignard solution from magnesium (5·0 g.), methyl iodide (29 g.), and ether (200 c.c.), and the mixture heated under reflux for 3 hours and worked up with ice and dilute sulphuric acid. Trituration of the gummy residue with light petroleum (b. p. 40—60°) gave 22 g. of the required *carbinol*, m. p. 85—90° (Found: C, 50·0; H, 4·4; Br, 41·4. $C_{16}H_{16}OBr_2$ requires C, 50·0; H, 4·2; Br, 41·7%).

4 : 4′-*Dibromo-αβ-dimethylstilbene and* 4 : 4′ : β : γ-*Tetrabromo-βγ-diphenyl*-n-*butane*.—The above carbinol (10 g.) was heated under reflux with acetyl chloride (10 c.c.) and acetic anhydride (10 c.c.) for 4 hours. The solvents were removed by distillation at 14 mm., and the residue distilled, b. p. 190—200°/0·5 mm., giving a thick oil (8 g.) which set, on cooling, to a glass. Dehydration with potassium hydrogen sulphate gave identical results. The product was dissolved in dry chloroform (10 c.c.) and treated with bromine (3·0 g.) in chloroform (10 c.c.). Removal of the solvent and excess of bromine at room temperature gave 4 : 4′ : β : γ-tetrabromo-βγ-diphenyl-*n*-butane, m. p. 180—185° (decomp.); mixed m. p. with an authentic specimen prepared from βγ-diphenyl-*n*-butane by bromination, 182—185°. Reduction of this compound in the manner described by Barber, Slack, and Woolman (*loc. cit.*) gave *cis*-4 : 4′-dibromo-αβ-dimethylstilbene, m. p. 86° (mixed m. p. with authentic sample, 87—90°).

4 : 4′-*Dibromo-α-ethyldeoxybenzoin* (XIX; R = Et).—4 : 4′-Dibromodeoxybenzoin (202 g.) was dissolved in alcohol (400 c.c.) containing sodium (13·3 g.). Ethyl iodide (90 g.) was added, and when the initial vigorous reaction had subsided further quantities of sodium (4·9 g.) in alcohol (100 c.c.) and ethyl iodide (33·7 g.) were added. After being heated under reflux for 5 hours, the reaction mixture was poured into water and kept overnight. The light brown solid was then collected and recrystallised from a large volume of methanol, giving 200 g. of the pure *deoxybenzoin*, m. p. 52° (Found: Br, 41·65. $C_{16}H_{14}OBr_2$ requires Br, 41·7%).

3 : 4-*Di*-(p-*bromophenyl*)-n-*hexan*-3-*ol* (XX; R = R′ = Et).—The α-ethyl compound (90 g.), dissolved in dry ether (350 c.c.), was added dropwise to a Grignard solution prepared from ethyl bromide (77 g.), magnesium (17·2 g.), and dry ether (1 l.). After being heated under reflux for 3 hours, the reaction mixture was worked up with ice and dilute sulphuric acid. Removal of the ether, and then of a small amount of 4 : 4′-dibromostilbene, m. p. 203°, followed by distillation of the residue, b. p. 206—210°/0·4 mm., gave the required *carbinol* as a pale yellow glass (Found : Br, 39·0. $C_{18}H_{20}OBr_2$ requires, Br, 38·8%). On standing, this deposited a crystalline compound (10 g.), apparently a solid modification of the carbinol, which can exist in a *meso*- and a racemic form. Crystallisation from ligroin (b. p. 60—80°) gave white needles, m. p. 160° (Found : Br, 38·9%).

4 : 4′-*Dibromo*-αβ-*diethylstilbene* (XXI; R = R′ = Et).—Dehydration of both forms of the above carbinol was carried out with both potassium hydrogen sulphate and acetic anhydride–acetyl chloride. In each case the same product, b. p. 200°/0·75 mm., was obtained as an almost colourless oil. On standing for many weeks, solidification slowly occurred and a solid (yield about one third of the weight of the oil) was collected and recrystallised from alcohol, forming white needles, m. p. 123° (Found : Br, 40·5. Calc. for $C_{18}H_{18}Br_2$: Br, 40·4%). The *trans*-4 : 4′-dibromodiethylstilbene described by Vargha and Kovács (*loc. cit.*) had m. p. 124°. On redistillation, the residual oil, b. p. 190—192°/0·5 mm., again deposited the same material, but much more slowly. All attempts to convert the oil into a homogeneous product by treatment with iodine in boiling nitrobenzene (to isomerise any *cis*-compound to the *trans*-form) failed.

4 : 4′-*Dicyano*-αβ-*diethylstilbene from the Dibromo-compound*.—The dibromo-compound (4·0 g.) was heated in boiling quinoline (20 c.c.) with cuprous cyanide (2·7 g.). After being worked up in the usual manner, the residual solid was sublimed repeatedly in a vacuum and finally recrystallised from ethanol, giving the dinitrile, m. p. 214—216°, identical with that previously described.

4 : 4′ : γ : δ-*Tetrabromo*-γδ-*diphenyl*-n-*hexane*.—4 : 4′-Dibromo-αβ-diethylstilbene (1·0 g.) was dissolved in dry chloroform (5 c.c.) and treated with bromine (0·6 g.) in chloroform (5 c.c.). Uptake of bromine was almost immediate in daylight, and removal of the solvent and excess of bromine at room temperature gave the *tetrabromo*-compound, m. p. 170° (decomp.) after recrystallisation from a very large volume of glacial acetic acid (Found : Br, 55·8. $C_{18}H_{16}Br_4$ requires Br, 55·8%).

4 : 4′-*Dibromo*-α-*benzyldeoxybenzoin*.—4 : 4′-Dibromodeoxybenzoin (10 g.) was dissolved in alcohol (12 c.c.) containing sodium (0·7 g.). Benzyl chloride (8·9 g.) was added, and when the initial reaction had subsided, this was followed by alcohol (4 c.c.) containing sodium (0·25 g.). Further benzyl chloride (3·3 g.) was then added and refluxing continued to neutrality. The reaction mixture was then poured into water, and the alcohol removed by distillation. Recrystallisation of the residue from alcohol gave the *product* (6·5 g.), m. p. 100—102° (Found : Br, 35·6. $C_{21}H_{16}OBr_2$ requires Br, 36·0%).

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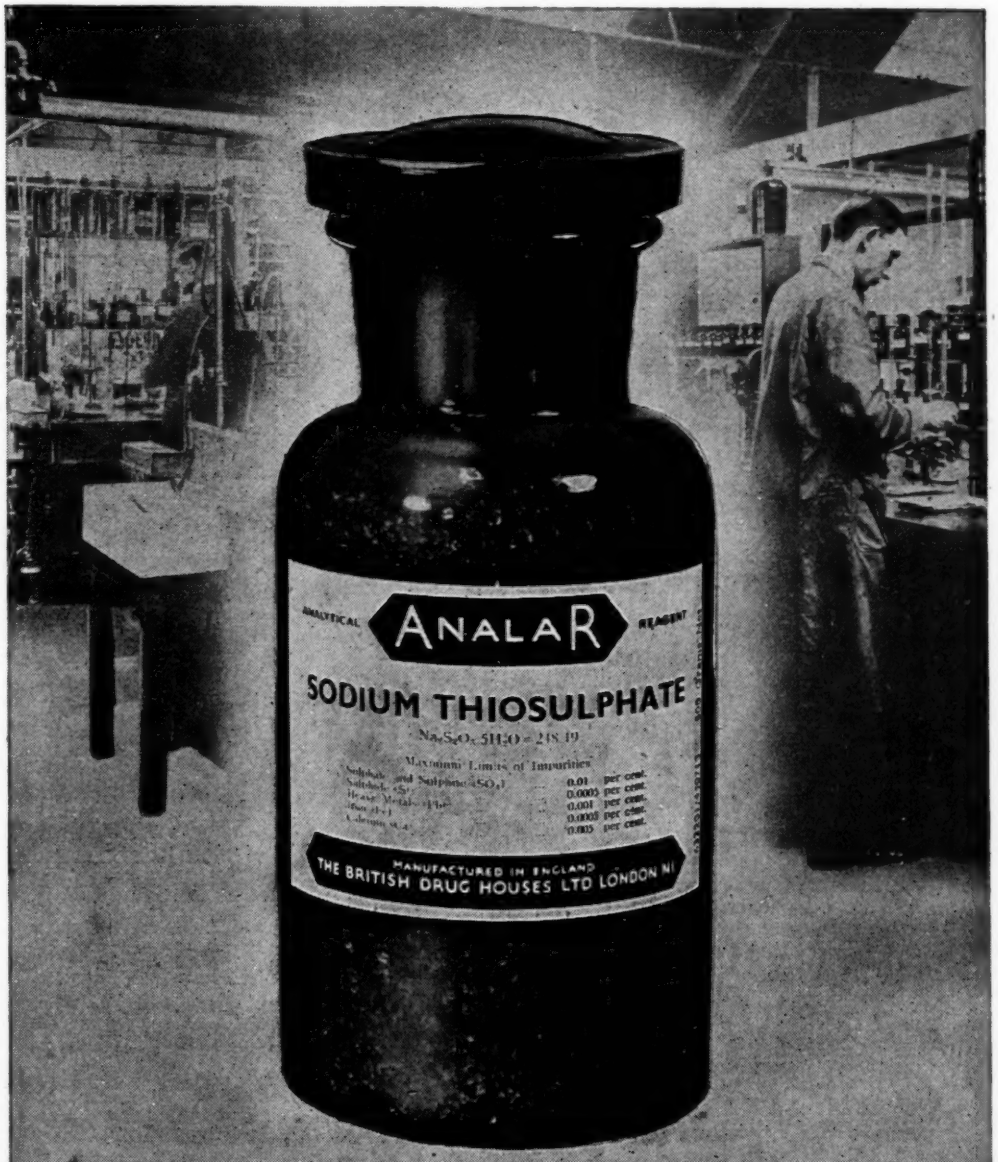

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